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CONTENTS OF VOLUME 68

JULY 1941. NUMBER 1

	PAGE
Thrombosis of the Deep Veins of the Leg: Its Clinical Significance as Exemplified in Three Hundred and Fifty-One Autopsies. Warren C. Hunter, M.D.; Vinton D. Sneed, M.D., and Thomas D. Robertson, M.D., Portland, Ore., and George A. C. Snyder, M.D., Spokane, Wash...	1
Serum Lipids in Patients with Rheumatoid Arthritis and in Patients with Obstructive Jaundice: A Comparative Study. Walter D. Block, Ph.D.; Oliver H. Buchanan, M.S., and Richard H. Freyberg, M.D., Ann Arbor, Mich.	18
Immediate Serum Reactions in Man: Classification and Analysis of Reactions to Intravenous Administration of Antipneumococcus Horse Serum in Cases of Pneumonia. David D. Rutstein, M.D.; Elizabeth A. Reed, B.A.; Alexander D. Langmuir, M.D., and Edward S. Rogers, M.D., Albany, N. Y.....	25
Torula Infection of the Lungs and Central Nervous System: Report of Six Cases with Three Autopsies. David L. Reeves, M.D.; E. M. Butt, M.D., and Roy W. Hammack, M.D., Los Angeles.....	57
Fusospirochetosis: Recovery of the Causative Organisms from the Blood, with Report of Two Cases. Robert H. Williams, M.D., Boston.....	80
Cause of the So-Called Side Ache that Occurs in Normal Persons: Personal Observations. Richard B. Capps, M.D., Chicago.....	94
Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers. Elaine P. Ralli, M.D.; Emanuel Papper, M.D.; Karl Paley, M.D., and Eli Bauman, M.D., New York.....	102
Hemorrhagic Diatheses: An Analysis of Three Hundred and Fifty-Five Autopsy Reports. Lawrence Perlman, M.D., and Theodore A. Fox, M.D., Chicago	112
Treatment of Lobar Pneumonia with Rabbit Antipneumococcus Serum: Efficacy of the Projected Dose Method of Treating Pneumonia with Homologous Refined and Unconcentrated Rabbit Antipneumococcus Serum. Elmer H. Loughlin, M.D.; Samuel H. Spitz, M.D., and Richard H. Bennett, M.D., Brooklyn.....	121
Progress in Internal Medicine:	
Metabolism and Diabetes: Review of Certain Recent Contributions. Edward H. Rynearson, M.D., and Alice G. Hildebrand, M.D., Rochester, Minn.....	134
Correspondence:	
Pinealectomies on Young Mammals. Loyal Davis, M.D., Chicago.....	176
Book Reviews.....	177

AUGUST 1941. NUMBER 2

Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock. Herrman L. Blumgart, M.D.; Monroe J. Schlesinger, M.D., and Paul M. Zoll, M.D., Boston.....	181
Differentiation of Intrahepatic and Extrahepatic Jaundice: Response of the Plasma Prothrombin to Intramuscular Injection of Menadione (2-Methyl-1,4-Naphthoquinone) as a Diagnostic Aid. Jere W. Lord Jr., M.D., and William DeW. Andrus, M.D., New York.....	199

AUGUST—*Continued*

PAGE

Treatment of Pneumococcic Meningitis with Sulfanilamide and Sulfapyridine: A Statistical Study of All Reported Cases in Which Chemotherapy Was Used, With or Without Specific Antipneumococcus Serum. Charles W. Steele, M.D., and Julius Gottlieb, M.D., Lewiston, Maine.....	211
Origin of Blood Amylase and Blood Lipase in the Dog: Relation Between Blood Amylase and Urinary Amylase Following Induction of Uranium Nephritis. Daniel L. Dozzi, M.D., Philadelphia.....	232
Clinical and Physiologic Characteristics of Chill. George A. Perera, M.D., New York.....	241
Studies on "Essential" Hypertension: II. The Association of Hypertension with Organic Renal Disease. Henry A. Schroeder, M.D., and J. Murray Steele, M.D., New York.....	261
The Blood Picture in Chickenpox. Arthur Andrews Holbrook, M.D., Milwaukee	294
Hepatic Function in Patients with Amyloidosis. Arthur Martin Tiber, M.D.; Alexander W. Pearlman, M.D., and Samuel E. Cohen, M.D., New York..	309
Progress in Internal Medicine:	
Infectious Diseases: A Review of Significant Publications in 1940-1941. Hobart A. Reimann, M.D., Philadelphia.....	325
News and Comment.....	369
Book Reviews.....	370

SEPTEMBER 1941. NUMBER 3

"Primary" Hypochromic Anemia Terminating in Pernicious Anemia: Report of Two Cases. Edward B. Miller, M.D., and William Dameshek, M.D., Boston	375
The Natural History of Bronchiectasis: A Clinical, Roentgenologic and Pathologic Study. Alan Gordon Ogilvie, M.D., M.R.C.P., Newcastle-on-Tyne, England.....	395
Blood Pressure Studies on West Indians and Panamanians Living on the Isthmus of Panama. B. H. Kean, M.D., Ancon, Canal Zone.....	466
Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis: I. Quantitative Effect of Diets Containing Ventriculin. Oliver P. Jones, Ph.D., Buffalo.....	476
State of Motor Centers in Circulatory Insufficiency. Ernst Simonson, M.D., and Norbert Enzer, M.D., Milwaukee.....	498
Acacia in Treatment of the Nephrotic Syndrome, with Special Reference to Excretion of Chloride and Water: A Report of Cases. Arnoldus Goudsmit Jr., M.D., Philadelphia, and Melvin W. Binger, M.D., and Norman M. Keith, M.D., Rochester, Minn.....	513
Diagnosis of Carcinoma of the Pancreas. J. Edward Berk, M.D., Philadelphia.	525
Primary Pulmonary Vascular Sclerosis. I. C. Brill, M.D., and John J. Krygier, M.D., Portland, Ore.....	560
Response of Normal Subjects to Acute Blood Loss, with Special Reference to the Mechanism of Restoration of Blood Volume. Richard V. Ebert, M.D.; Eugene A. Stead Jr., M.D., and John G. Gibson II, M.D., Boston.....	578
Clinical Lipoid Nephrosis, with Special Reference to Its Transformation into Clinical and Pathologic Chronic Glomerulonephritis. George G. Gilbert, M.D., Durham, N. C.....	591
Progress in Internal Medicine:	
Vascular Diseases: Seventh Annual Review. George W. Scupham, M.D.; Géza de Takáts, M.D.; Theodore R. Van Dellen, M.D., and Joseph H. Jesser, M.D., Chicago.....	599
News and Comment.....	661
Book Reviews.....	662

OCTOBER 1941. NUMBER 4

	PAGE
Bronchiolitis Fibrosa Obliterans: Report of a Case. John S. LaDue, M.D., New Orleans.....	663
Origin of Ketone Bodies From Fats and Their Regulation. Samuel Soskin, M.D., and R. Levine, M.D., Chicago.....	674
Acropachyderma with Pachydermiostitis: Report of a Case. Heinrich G. Brugsch, M.D., Boston.....	687
Acacia in the Treatment of the Nephrotic Syndrome: Influence of Acacia, Injected Intravenously, on Concentration of Proteins and on Colloid Osmotic Pressure of the Serum. Arnoldus Goudsmit Jr., M.D., Philadelphia, and Melvin W. Binger, M.D., and Marschelle H. Power, Ph.D., Rochester, Minn.....	701
Adrenocortical Compounds in the Blood: Relation of Their Quantity to Arterial Hypertension, Renal Insufficiency and Congestive Heart Failure. W. Raab, M.D., Burlington, Vt.....	713
Determination of Urobilinogen in Feces and in Urine: A Comparison of the Sparkman and the Watson Procedure. C. J. Watson, M.D., and Eleanor Bilden, Minneapolis.....	740
Direct Cultivation of Bacterium Tularensis from Human Blood Drawn During Life and at Autopsy: Report of Three Fatal Cases of Tularemia, with Brief Notes on Two Others. John C. Ransmeier, M.D., Nashville, Tenn., and Isabelle G. Schaub, B.A., Baltimore.....	747
Progress in Internal Medicine:	
Gastroenterology: A Review of Literature from July 1940 to July 1941. Chester M. Jones, M.D., Boston.....	763
News and Comment.....	846
Book Reviews.....	847

NOVEMBER 1941. NUMBER 5

Significance of Bacteremia Caused by Staphylococcus Aureus: A Study of One Hundred and Twenty-Two Cases and a Review of the Literature Concerned with Experimental Infection in Animals. David Skinner, M.D., and Chester S. Keefer, M.D., Boston.....	851
Metabolism in Organic Hyperinsulinism: I. Quantitative Studies of the Variations in the Rate of Combustion of Carbohydrate Produced by Alterations in the Diet. Jerome W. Conn, M.D., and Elizabeth Stern Conn, M.D., Ann Arbor, Mich.....	876
Blood Sugar in a Case of Complete Hypophysectomy. James Finlay Hart, M.D., and Morton Magiday, M.D., New York.....	893
Biologic False Positive Serologic Reactions in Tests for Syphilis: I. Occurrence in Normal Persons. Charles F. Mohr, M.D.; Joseph Earle Moore, M.D., and Harry Eagle, M.D., Baltimore.....	898
Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: I. Immediate Prognosis. Francis F. Rosenbaum, M.D., Ann Arbor, Mich., and Samuel A. Levine, M.D., Boston	913
Importance of the Dextrose Tolerance Test in the Diagnosis of Marginal Malnutrition. G. Wilse Robinson Jr., M.D.; Prior Shelton, M.D., and Frank V. Smith Jr., A.B., Kansas City, Mo.....	945
Acute, Massive Hemoglomerinuria of Obscure Cause, with Jaundice and Anemia: Report of a Case with Clinical and Hematologic Studies and Measurements of the Blood Pigment Metabolism. Mark D. Altschule, M.D., and D. Rourke Gilligan, M.S., Boston.....	957

NOVEMBER—*Continued*

Progress in Internal Medicine:	PAGE
Diseases of the Adrenal Glands:	
I. Addison's Disease. Edwin J. Kepler, M.D., and Donald M. Willson, M.D., Rochester, Minn.....	979
II. Tumors of the Adrenal Cortex, Diseases of the Adrenal Medulla and Allied Disturbances. Edwin J. Kepler, M.D., and F. Raymond Keating, M.D., Rochester, Minn.....	1010
Correspondence:	
Chemical Factors in the Formation of Gallstones. Louis Bauman, M.D., New York, and Joseph T. Bashour, Ph.D., Richmond Hill, N. Y....	1037
News and Comment.....	1039
Book Reviews.....	1040

DECEMBER 1941. NUMBER 6

Elliptic Erythrocytes in Man. Helen Wyandt, M.S., Omaha; Paul M. Bancroft, M.D., Lincoln, Neb., and Theodore O. Winship, M.D., Rizal, Philippine Islands.....	1043
Efficacy of Intravenous Sodium Bicarbonate Therapy in the Treatment of Diabetic Ketosis. Louis B. Owens, M.D.; Jackson Wright, M.D., and Edna Brown, M.S., Cincinnati.....	1066
Rheumatic Pneumonia. Emanuel Z. Epstein, M.D., and Edward B. Greenspan, M.D., New York.....	1074
Tuberculoma of Hypophysis with Insufficiency of Anterior Lobe: A Clinical and Pathologic Study of Two Cases. Jack D. Kirshbaum, M.D., and Herman A. Levy, M.D., Chicago.....	1095
Metabolism in Organic Hyperinsulinism. Jerome W. Conn, M.D., and Elizabeth Stern Conn, M.D., Ann Arbor, Mich.:	
II. Effects of Epinephrine on Glycemic Level and on Combustion of Carbohydrate.....	1105
III. Effects of Adrenal Cortical Extract on Blood Sugar and on Sodium and Nitrogen Equilibrium.....	1115
Hypothermia: Report of a Case in Which the Patient Died During Therapeutic Reduction of Body Temperature, with Metabolic and Pathologic Studies. John H. Talbott, M.D.; W. V. Consolazio, B.S., and L. J. Pecora, B.S., Boston.....	1120
Therapy of Tetanus: A Study of Two Hundred and Seventy-Six Cases. Ralph Spaeth, M.D., Chicago.....	1133
Biologic False Positive Serologic Reactions in Tests for Syphilis: II. Occurrence with Organic Diseases Other Than Syphilis. Charles F. Mohr, M.D.; Joseph Earle Moore, M.D., and Harry Eagle, M.D., Baltimore..	1161
Pulmonary Cavitation Associated with Coccidioidal Infection. William A. Winn, M.D., Springville, Calif.....	1179
Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: II. Ultimate Prognosis. Samuel A. Levine, M.D., Boston, and Francis F. Rosenbaum, M.D., Ann Arbor, Mich.	1215
Progress in Internal Medicine:	
Review of Neuropsychiatry for 1941. Stanley Cobb, M.D., Boston.....	1232
Book Reviews.....	1246
General Index.....	1247

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THROMBOSIS OF THE DEEP VEINS OF THE LEG

ITS CLINICAL SIGNIFICANCE AS EXEMPLIFIED IN THREE
HUNDRED AND FIFTY-ONE AUTOPSIES

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Generally accepted facts are not invariably supported by published data. The voluminous literature on venous thrombosis contains surprisingly little pertaining to the deep veins of the calf. This is scarcely attributable to ignorance or to a lack of appreciation of phlebothrombosis in this part of the body. Experienced necroscopists have long been aware that the legs constitute a common, though often clinically silent, reservoir of clot formation during life and at autopsy seek here when other more readily accessible sources of embolism have failed. Rather, it appears to us that such factors as antagonism on the part of embalmers toward extensive dissection, restrictions imposed by relatives and ambiguity or possible interpretations of the laws pertaining to mutilation may be more potent reasons for the paucity of figures with respect to this part of the body.

Much credit for the recognition of the common occurrence and the clinical importance of venous thrombosis in the calf of the leg belongs to Jakob Erdheim of Vienna. Not a prolific writer, Erdheim seems to have confined his observations on this particular subject to his lectures and demonstrations. Even so, his emphatic insistence that the veins of

Read at a meeting of the American Association of Pathologists and Bacteriologists, Pittsburgh, March 22, 1940.

From the Department of Pathology, University of Oregon Medical School, and the Pathological Laboratories of St. Vincent's Hospital, Portland, and Western State Hospital, Fort Steilacoom, Wash.

the leg constitute a most important source of pulmonary emboli made an indelible impression on listeners,¹ and by them the information has been passed on to many others.

A survey of the literature indicates that only Rössle,² Neumann³ and Frykholm⁴ have accumulated any considerable data bearing directly upon the postmortem incidence of thrombosis of the veins of the calf. More extended reference to the work of these men will be found in the comment in the present communication.

MATERIAL AND METHODS

Prompted by a desire for firsthand knowledge and with the feeling that easily accessible statistics in English might be appreciated by others, we routinely removed the soleus and gastrocnemius muscles from as many as possible of an unselected group of patients, both adolescents and adults, on whom autopsies were performed over a period beginning with March 1939 and extending well into February of the following year. In order to ascertain whether venous thrombosis was more frequent in one type of hospital than in another, cooperative effort was resorted to, and material was accumulated from (1) a charity hospital, (2) a state psychopathic institution and (3) two private hospitals.

Removal of the muscles was accomplished through a lateral incision extending from the ankle to above the knee; we carefully dissected the muscles from the posterior aspect of the leg bones and were certain to detach high enough to catch the heads of the gastrocnemius muscle and as much of the popliteal vein as possible. The specimens, properly labeled, were fixed by suspension in large crocks of solution of formaldehyde and then sectioned transversely at intervals of approximately 2 cm. The frequent variations in color and consistency of the clots often made necessary the taking of several blocks at different levels along the muscles and from various veins. Identification as to source was carried through to the microscopic sections. Individual macroscopic descriptions were made in all instances. Specimens exhibiting empty veins or containing only fluid blood were not studied microscopically. On this basis 209 pairs of muscles were subjected to microstudy, with the result that thrombi of varying age proved to be present in 52.7 per cent of the whole group of 351 patients (table 1).

While we were cognizant of Neumann's³ observations concerning the frequency of thrombi in the plantar veins, it was deemed inadvisable, except in a very few instances, to go any farther than the legs for fear of losing the good will of the embalmers. For the same reason we did not attempt to dissect the veins of the thigh; so our observations of the femoral veins were of necessity confined to the part accessible from the abdomen. On the other hand, a conscious effort was made throughout to search carefully for venous thrombi in all parts of the body ordinarily examined at autopsy.

1. Osgood, E. E.: Personal communication to the authors, 1928. Menne, F. R.: Personal communication to the authors, 1931.

2. Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, *Virchows Arch. f. path. Anat.* **300**:180, 1937.

3. Neumann, R.: Ursprungszentren und Entwicklungsformen der Bein-Thrombose, *Virchows Arch. f. path. Anat.* **301**:708, 1938.

4. Frykholm, R.: Pathogenesis in Venous Thrombosis and Mechanical Prophylaxis, *Nord. med. (Hygiea)* **4**:3534, 1939.

TABLE 1.—*Summary of Data on Autopsies of Three Hundred and Fifty-One Unselected Patients*

	Hospital				
	MCH*	SV†	WS‡	PS§	Total
Total number of autopsies.....	200	61	55	35	351
Number of patients with thrombosis of leg veins (thrombus subgroup)	118	30	23	14	185
Percentage of occurrence of thrombosis.....	59%	49%	41.8%	40%	52.7%
Total number of patients with fatal pulmonary emboli...	7	4	0	0	11
With fatal emboli from leg veins alone.....	4	1	0	0	5
With fatal emboli possibly from other than leg veins.	2	2	0	0	4
With fatal emboli not from leg veins.....	1	1	0	0	2
Percentage of deaths in whole group.....	3.5%	6.5%	3.13%
Percentage of deaths in thrombus subgroup.....	5.09%	10.0%	4.8%
Deaths of medical patients.....	4	2	0	0	6
Deaths of surgical patients.....	3	2	0	0	5
Males with fatal pulmonary emboli.....	5	4	0	0	9
Females with fatal pulmonary emboli.....	2	0	0	0	2
Total number of patients with nonfatal emboli.....	24	3	7	6	40
With infarction	5	2	1	2	10
Without infarction	19	1	6	4	30
Percentage of patients with nonfatal emboli in whole group	12%	4.9%	12.7%	17.1%	11.39%
Percentage of patients with nonfatal emboli in thrombosis subgroup	20.3%	9.67%	30.4%	42.8%	20.5%
Males with nonfatal pulmonary emboli.....	12	3	5	0	20
Females with nonfatal pulmonary emboli.....	12	0	2	6	20
Percentage of patients with pulmonary emboli in whole group	15.5%	11.4%	12.7%	17.1%	14.55%
Total number of patients with thrombi occurring elsewhere	22	8	10	3	43
In thrombus subgroup with thrombi elsewhere.....	19	5	6	2	32
Not included in thrombus subgroup.....	3	3	4	1	11
Service classification					
Number of surgical patients in whole group.....	29	12	2	9	52
Number of medical patients in whole group.....	159	43	52	26	280
Number of patients in both surgical and medical or in undetermined services in whole group.....	12	6	1	0	19
Number of surgical patients in thrombus subgroup....	16	3	1	4	24
Number of medical patients in thrombus subgroup....	95	22	22	10	149
Number of patients in both surgical and medical or in undetermined services in thrombus subgroup.....	7	5	1	0	13
Percentage of surgical patients with thrombi in leg veins	55.2%	25.0%	50.0%	44.4%	46.9%
Percentage of medical patients with thrombi in leg veins	59.7%	51.1%	42.3%	38.4%	53.2%
Percentage of patients in both surgical and medical or in undetermined services with thrombi in leg veins... 53.3%	53.3%	83.3%	100%	68.4%
Sex classification					
Number of males in whole group.....	131	43	38	12	224
Number of females in whole group.....	69	18	17	23	127
Percentage of males in thrombus subgroup.....	60.3%	46.5%	39.4%	25.0%	52.2%
Percentage of females in thrombus subgroup.....	56.5%	55.5%	47.0%	47.8%	53.5%
Incidental findings					
Number of patients with edema in whole group.....	73	9	11	10	103
Number of patients with edema in thrombus subgroup	48	8	8	6	70
Number of patients with muscle atrophy in whole group	71	19	23	9	122
Number of patients with muscle atrophy in thrombus subgroup	46	16	11	5	78
Number of patients with phlebitis in whole group.....	9	2	4	2	17
Number of muscles studied microscopically.....	151	30	9	19	209
Percentage of occurrence of phlebitis in muscles sectioned	5.9%	6.6%	13.8%	10.5%	8.1%
Age grouping					
Oldest patient with thrombosis of leg veins.....	94	86	92	84	94
Youngest patient with thrombosis of leg veins.....	15	30	27	46	15
Average age of patients with thrombosis of leg veins..	65.4	59.9	69.9	67.5	64.9
Oldest patient in whole group.....	94	86	92	84	94
Youngest patient in whole group.....	15	15	27	29	15
Average age of patients in whole group.....	60.8	55.8	65.9	57.6	59.78

* MCH, Multnomah County Hospital, Portland.

† SV, St. Vincent's Hospital, Portland.

‡ WS, Western State Hospital, Washington.

§ PS, Portland Sanitarium and Hospital, Portland.

For a time the circumference of the calves was measured, but the procedure was later abandoned, for the reason that the legs had not been measured when the patients first took to bed and there was therefore no basis for comparison. Furthermore, it was found that the size of the two legs was likely to be the same even when there was unilateral thrombosis.

GENERAL CONSIDERATIONS

To one unfamiliar with the anatomy of the muscles of the calf it is a distinct surprise to observe the number and size of their veins. Often the posterior tibial and peroneal arteries are paralleled by three or four *venae comitantes*. Within the substance of the muscles veins are plentiful and if distended stand out strikingly in cross sections. Likewise, the small but numerous *venae surales* of the heads of the *gastrocnemius* muscle are readily seen when filled with blood. Not uncommonly veins along the arteries and in the soleus muscle attain a diameter of 10 or even 15 mm. Sclerosis is infrequent; so empty veins collapse readily and give an erroneous impression of being normally small. Occasional valves are demonstrable in the major veins. Tributaries to large veins usually enter at a right angle.

After a little experience one has no difficulty in distinguishing between fresh thrombi and postmortem clots. Since the propagated part of a thrombus and a postmortem clot may look alike, it is essential that one follow such clots serially by means of transverse cuts. Frequently the character will change to that of an unmistakable thrombus caudal to where the clot is first encountered. Often an apparently unchanged and even empty vein of large caliber will show one or more tributaries occluded by thrombi whose ends protrude for a little way into the lumen of the parent vessel. It is difficult to escape the conviction that such unsupported clots are not a prolific source of small emboli. Another variation of progressive thrombosis in the direction of the heart is a gradual inward-building of the clot from the periphery, leaving an opening at the middle. Apparently organization of thrombi in the deep veins of the leg proceeds rather slowly and haltingly, since one often has the experience of seeing segments several centimeters long literally pop out of freshly transected veins without one's having exerted any appreciable pressure on the muscle. Unless this fact is appreciated, whole thrombi may be lost or discarded as of no importance.

As a rule, if thrombi exist at all more than one vein will be involved and the process will be bilateral. The veins accompanying the larger arteries and those within the soleus muscle are much more often occluded than are those of the *gastrocnemius* muscle, the ratio in our series being about 2 to 1 (table 2). Almost any portion of the soleus muscle may be the seat of thrombi, but in the *gastrocnemius* muscle the clots are likely

to be limited to the heads of the muscle or the area near the insertion of the achilles tendon. There is a slight predilection for the right side in unilateral thrombosis (table 2).

TABLE 2.—*Location and Number of Thrombosed Leg Veins*

	Multnomah County Hospital	St. Vincent's Hospital	Western State (Wash.)	Portland Sanitarium and Hospital	Totals
Bilateral.....	69	20	10	11	110
Unilateral.....	49*	10	13	3	75
Right soleus muscle.....	95	24	12	14	145
Left soleus muscle.....	87	26	12	11	136
Right gastrocnemius muscle.....	36	10	12	3	61
Left gastrocnemius muscle.....	36	10	6	3	55

* Among the 118 patients with thrombosis were 7 in whom one leg had been amputated. Thus it is possible that unilateral involvement is higher than might have been the case had both legs been present.

TABLE 3.—*Pertinent Data on Eleven Instances of Fatal Pulmonary Embolism*

Sex	Age	Primary Condition of Patient	Medi- cal	Surg- ical	Location of Pulmonary Emboli	Source of Pulmonary Emboli	State of Deep Veins of Leg	Days in Bed
M	89	Infection of hand; infarction, lower lobe of left lung	..	+	Both main branches	Leg veins alone	Thrombosis, right leg only	22
M	85	Old coronary throm- bosis and infarction with aneurysm; con- gestive heart failure	+	..	Either main branch	Leg veins alone	Thrombosis, bilateral	25
M	67	Carcinoma of rec- tum, resected; fecal fistula	..	+	Both main branches	Leg veins alone	Thrombosis, bilateral	16
M	51	Coronary thrombo- sis; infarction, left ventricle	+	..	Main branches	Leg veins alone	Thrombosis, bilateral	123
M	64	Bilateral inguinal hernia; herni- orrhaphy	..	+	Main artery and both branches	Left femoral, iliac or leg veins	Thrombosis, left leg only	15
M	64	Prostatic hyper- plasia with obstruc- tion; pyelonephritis	+	..	Both main branches	Leg veins alone	Thrombosis, left leg only	2
F	51	Recent hysterec- tomy; thrombosis of pelvic veins	..	+	Main artery and both branches	Iliac veins, inferior vena cava or leg veins	Thrombosis, bilateral	13
M	73	Thrombophlebitis, right iliac, femoral and superficial veins	+	..	Main artery and both branches	One or more of involved veins	Thrombosis, bilateral	6
F	71	Carcinomatosis; marked coronary arteriosclerosis	+	..	Main artery	Veins of broad ligaments	No thrombi	3
M	34	Recent gastric resection	..	+	Main artery	Left internal iliac vein	No thrombi	13
M	70	Thyrototoxic heart with congestive heart failure	+	..	Right main branch	Right atrium or leg veins	Thrombosis, left leg only	13
M, 9 F, 2	6 54.5%	5 45.5%	From leg veins, 5, 45.4% Likely not from leg veins, 4, 36.3% Not from leg veins, 2, 18.2%			

In a large series one may rightly anticipate the finding of thrombi of all ages, but in our experience the great majority were either fresh or in the stage of softening and early organization, and their age tended to

parallel the length of time in bed. Only occasionally will canalized thrombi alone exist, and in such cases reference to the clinical record will sometimes elicit the information that the patient has had a prior confinement. Ancient thrombi are easily recognized macroscopically either by a rusty brown color or by a form of fenestration that is different from the diffuse sievelike openings in canalized arteries. The openings are always situated at the periphery around an almost solid, white, central plug, in a fashion simulating a spoked wheel. The size of the channels is surprisingly great. In some instances the degree of thrombus formation is minimal; perhaps it is limited to one small vein or, in the case of larger vessels, to the sinuses behind the valves. In the latter instance, when the thrombi organize the valves become fixed and functionless in the same manner as those Edwards and Edwards⁵ produced experimentally.

ANALYSIS OF FINDINGS

Although the essential data have been put in tabular form, certain features deserve amplification.

Age.—Both the youngest, 15 years, and the oldest, 94 years, of the patients displayed thrombosis. The average age of the whole group was 59.78 years; for the 185 persons in whom occlusion was found in a leg vein the average age was 64.9 years. The difference is not impressive.

Sex.—The ratio of nearly 2 males to 1 female is a chance figure, yet one which from year to year tends to remain fairly constant, probably because it seems to be easier to obtain permission for autopsy on males. The frequency of thrombosis was practically the same—52.2 per cent in males and 53.5 per cent in females.

Service Classification.—Of all the patients, 79.7 per cent were medically treated, and 14.8 per cent were surgically treated; a third category, termed “mixed,” was required to classify 5.4 per cent of the patients suffering from both medical and surgical conditions and treated accordingly. As between the strictly medical and surgical patients there was little difference in the incidence of thrombosis, for of the former 53.2 per cent and of the latter 46.9 per cent had demonstrable thrombi in the veins of the calf. In the “mixed” category the incidence of thrombosis was significantly higher, amounting to 68.4 per cent.

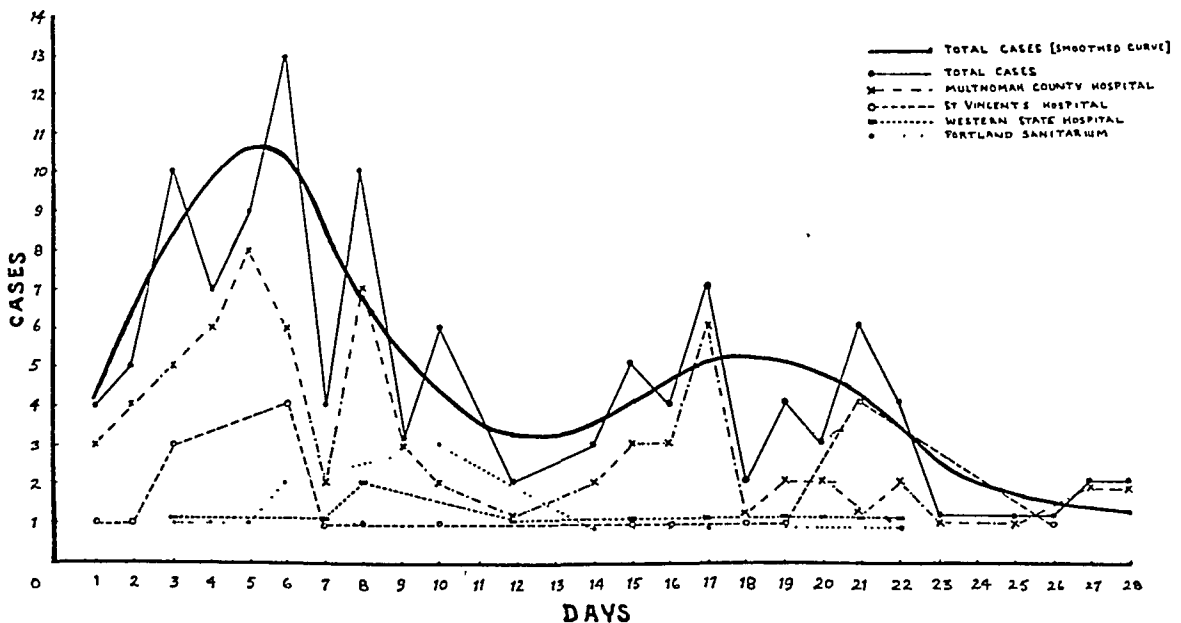
Time in Bed.—As might be anticipated for a group of this size in which the patients came from widely different types of hospitals, the period of recumbency ranged from one day (a single patient suffering from severe burns) to seven years (1 patient). However, as shown in

5. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Valve, Surg., Gynec. & Obst. **65**:310, 1937.

the combined curve (chart 1), the great majority of deaths occurred within four weeks after admission and the curve had two peaks, one during the fifth and sixth days and one during the third week. It should be emphasized that all of the 351 patients were almost continuously bedridden from the time of entry to death.

Fatal Pulmonary Embolism.—Eleven, 3.13 per cent, of the entire group died as a direct result of pulmonary embolism. Of these, 6 were medical patients and 5 were surgical patients; 9 were male and the other 2 were female, or, putting it differently, 4.01 per cent of all males died from pulmonary embolism, in contrast to 1.57 per cent of all females.

If the veins of the thigh and the plantar veins, which we could not examine, are left out of consideration, it would appear that among the



As indicated by the composite curve, the greatest number of deaths among persons found to have thrombosed leg veins occurred during the last half of the first and in the third week in the hospital.

11 fatalities from embolism, the most probable point of origin was from thrombi in the veins of the calf in 5 instances (45.4 per cent). The pulmonary emboli found were of such diameter, length and age as to mirror those still remaining in the legs. Multiple emboli were far more common than single massive clots. There were 4 instances (36.3 per cent) in which the lethal emboli could have come from thrombosed leg veins, but the presence of other thrombi either in large veins nearer the heart or within its right chambers seemed to be more likely sources. In only 2 of the 11 there were no thrombi in the leg veins; in 1 of these the emboli came from the veins of the broad ligaments and in the other from an internal iliac vessel. Circulatory failure on a cardiac basis was present in 4 of the 6 medical patients but was not a factor in the deaths of the surgical patients. Computed on the 185 instances of phlebothrom-

bosis of the legs, 4.8 per cent of the deaths in this subgroup were due to pulmonary embolism.

Nonfatal Pulmonary Embolism.—This condition was found in 40 patients. In 10 of these the emboli occluded branches large enough to bring about infarction; in the remainder they were either too small or of too recent origin to have caused necrosis. Some were discovered only by opening the smaller pulmonary branches according to the German technic recently reemphasized by Belt.⁶ It is interesting to note that, although 11.39 per cent of all patients examined showed nonfatal emboli, the figure almost doubles (20.5 per cent) in the subgroup of 185 patients

TABLE 4.—*List of the Venous Thrombi, Exclusive of Those in the Deep Veins of the Leg, Occurring in Three Hundred and Fifty-One Unselected Necropsies*

Periurethral vein	1
Periurethral vein and saphenous parva.....	1
Periprostatic vein	7
Periprostatic vein and right atrium.....	2
Periprostatic vein and inferior vena cava.....	1
Periprostatic vein, inferior vena cava, left iliac vein.....	1
Veins of the broad ligaments.....	3
Veins of the broad ligaments and varicose veins of the leg....	1
Iliac veins	2
Inferior vena cava	2
Portal vein	2
Renal vein	1
Right atrium, right ventricle or both.....	5
Varicose veins of legs.....	3
Popliteal vein	1
Popliteal and posterior veins of thighs.....	1
Saphenous parva, left.....	2
Superficial veins about an ulcer of the leg.....	1
Femoral vein (in aneurysm only).....	1
Plantar veins	1
Pulmonary arteries (primary thrombosis).....	2
Thyroid veins (post-thyroidectomy).....	1
Cavernous sinus	1
Total.....	43

whose leg veins were thrombosed. Smaller emboli were discovered in 20 males and in an equal number of females, although on a percentage basis, since males outnumbered females about 2: 1, small emboli proved almost twice as common in females (15.7 per cent) as in males (8.9 per cent). This is diametrically opposed to what took place with fatal embolism. If cases both of fatal and of nonfatal embolism are added together, the total incidence of pulmonary embolism becomes 14.55 per cent.

Other Thrombi.—A total of 32 patients displayed thrombosis in parts of the body in addition to the leg veins; 11 others showed no involvement of the veins of the calf but harbored clots in other locations. It would thus appear that when venous thrombosis occurs there is a strong probability that the deep vessels of the leg will be one of the sites. The several locations of thrombi outside the legs are listed in table 4.

6. Belt, T. H.: Demonstration of Small Pulmonary Emboli at Autopsy, J. Tech. Methods 15:39, 1936.

Phlebitis.—There has long been a tendency to speak of phlebothrombosis and phlebitis as synonymous states. This, we feel, is a mistake. During the process of resorption of a clot one not infrequently observes monocytes and lymphocytes along with blood pigment within the walls of the vein. There can be no doubt that the function of the monocytes is to engulf the blood pigment. While the purpose of the lymphocytes is not clear, we doubt that they represent an inflammatory reaction, or if so, they represent a secondary phenomenon and bear no causal relationship to thrombus formation. The diagnosis of acute phlebitis is hazardous in the absence of polymorphonuclear leukocytes. Among the 209 specimens from which blocks of the leg muscles were studied histologically, phlebitis was discovered only 17 times (8.1 per cent), and even this small figure becomes less significant when the details of individual instances are given. Thus, in a patient with carcinoma of the sigmoid flexure of the colon and peritonitis the left femoral vein but not the veins of the legs revealed inflammation; a patient suffering from pulmonary and intestinal tuberculosis had phlebitis of one femoral vein only; in the same category was a man with osteomyelitis and phlebitis of one common iliac vein; a fourth patient, dying from congestive heart failure, exhibited inflammation of a superficial varicose vein of the leg, while the deep vessels escaped. If these patients are eliminated, the occurrence of phlebitis involving the veins of the calf amounts to only 6.2 per cent, and in 2 of the remaining 13 patients no thrombi were present. In 1, the process was focal and minimal in that only part of the circumference of a single vein was involved; in the other, a woman dying of subacute bacterial endocarditis, there was nothing more than an extension from the popliteal artery which had become blocked by a septic embolus, probably through the medium of the communicating vessels recently described by Winternitz and Le Compte.⁷ The vein was not occluded. Among those with phlebitis of the veins of the calf were a patient who died of generalized peritonitis complicating a ruptured appendix, in whom only the outer part of the vein wall was affected, and a patient with a fracture of the femur, in whom the femoral vein and the veins of the calf on the injured side were the seat of phlebitis. Six times acute or subacute inflammation was concurrent with thrombosis of the leg veins, but always the process was either focal or slight, and the clots at this level were bland. Two examples of phlebitis were quite different from the others. One occurred in a woman who had streptococcic cellulitis of the thigh for which she was put to bed for fifty-two days and in whom the veins of the soleus muscles were both thrombosed and inflamed. The other was seen in a 73 year old man who had a primary phlebitis of the right

7. Winternitz, M. C., and Le Compte, P. M.: Experimental Infectious Angiitis, *Am. J. Path.* **16**:1, 1940.

iliac, femoral and superficial veins for which he had been in bed six days. Phlebitis was marked on the affected side, and the leg veins were occluded. Our experience leads to the conclusion that so far as the veins of the calf are concerned phlebitis has little to do with thrombus formation.

Edema.—Altogether, 103 patients with edema affecting the legs alone or with generalized edema were encountered, a percentage of 29.3. Among these were 70 (37.3 per cent) in whom the deep vessels of the calf were blocked by thrombi. It is doubtful if edema per se bears any relation to phlebothrombosis, since it is only a little more frequent among

TABLE 5.—*Clinical Grouping of Cases*

Clinical Service and Group	MCH*	SV†	WS‡	PS§	Total
Cardiovascular					
In whole group.....	83	17	19	11	130
In thrombus subgroup.....	48	9	7	5	69
Percentage with thrombosis.....	57.7	52.9	36.8	45.4	53.07
Infection					
In whole group.....	55	14	17	13	99
In thrombus subgroup.....	32	7	10	4	53
Percentage with thrombosis.....	58.18	50.0	58.8	30.7	52.5
Cachexia					
In whole group.....	34	17	8	6	65
In thrombus subgroup.....	22	8	2	5	37
Percentage with thrombosis.....	64.7	47.05	25.0	83.3	56.9
Obstructions					
In whole group.....	10	3	2	0	15
In thrombus subgroup.....	5	0	1	0	6
Percentage with thrombosis.....	50.0	50.0	40.0
Miscellaneous					
In whole group.....	18	9	9	5	41
In thrombus subgroup.....	11	6	3	0	20

* MCH, Multnomah County Hospital, Portland.

† SV, St. Vincent's Hospital, Portland.

‡ WS, Western State Hospital, Washington.

§ PS, Portland Sanitarium and Hospital, Portland.

persons with involvement of the veins in the leg than in those without thrombosis there. In most instances the edema could be ascribed to cardiac weakness.

Atrophy of Leg Muscles.—The possibility that atony or atrophy might predispose to thrombosis in a situation where adequate venous function depends on muscular activity as well as on gravity led us to note the gross and microscopic state of the muscle fibers. Atrophy was demonstrable in 122 patients (34.7 per cent) out of the whole group; 78 of these (63.9 per cent) had thrombosed leg veins, a difference of 29.2 per cent. Since the material was seen only at autopsy the factor of atony could not be evaluated.

Clinical Grouping.—With the hope of ascertaining whether clot formation in the leg veins was more frequent in one clinical condition than

in another, an attempt was made to segregate the cases of these patients according to the major conditions found. All too often there was troublesome overlapping, and we were forced to catalogue 41 cases as "miscellaneous." Perhaps a better designation would be "mixed." The figures obtained have been included for what they may be worth (table 5). Leaving this miscellaneous category out of consideration, we were surprised to learn that venous thrombosis in the calf occurs almost equally commonly among persons with cardiovascular diseases, infections or cachexias. In the obstructive category were the cases of 15 patients suffering from hyperplasia of the prostate gland or lesions of the bowel, uncomplicated by infection or cachexia, 40 per cent of whom had phlebotrombosis. Again we would emphasize that the one factor common to all, with or without thrombosis, was continuous rest in bed for varying periods of time without the benefit of planned and systematic exercise.

COMMENT

Presumably to test the validity of clinical evidence of frequent thrombosis of the plantar veins and the deep veins of the legs, Rössle,² in 1937, dissected the legs and thighs of 324 persons over 20 years of age who came to necropsy. Of these, 88 (27.1 per cent) harbored thrombi in the veins of the calf. Concomitant thrombosis in the femoral vein and the veins of the calf was found 38 times; on the other hand, there were only 7 instances of involvement of the femoral or hypogastric veins in the absence of thrombosed leg veins. Rössle raised the question as to whether the leg veins can be the source of pulmonary emboli, as occasionally happens in like-sized vessels, such as the pelvic veins. It was his feeling that emboli originating from the leg veins rarely become fatal but are nevertheless significant in that they tend to extend on into the femoral and iliac veins, from which the fulminating emboli originate. Even so, in carefully dissected preparations Rössle observed 3 instances in which massive pulmonary obstruction could be accounted for only on the basis of antemortem clots located in the veins of the calf. Frequently associated with the thrombosis were degenerative and atrophic changes in the leg muscles, and for this association Rössle offered three possible explanations: (1) that the alterations are due to thrombosis, against which is the fact that the clots are usually more recent than the changes in the muscles; (2) that degeneration of the muscles leads to the formation of substances causing clotting, and (3) that the two processes are independent, although perhaps the result of a common cause.

Voegt⁸ further investigated Rössle's material, paying especial attention to the effects of long confinement in bed. The calf muscles and the

8. Voegt, H.: Veränderungen der Wadenmuskulatur bei Venenthrombose und langem Frankengericht, *Virchows Arch. f. path. Anat.* **300**:190, 1937.

rectus abdominis and biceps muscles from the same subjects were compared histologically. Five persons with thrombosed leg veins showed degenerative phenomena and atrophy of the muscles, but 22 others, likewise bedridden for a long time, had equally severe alterations of the leg muscles in the absence of thrombosis. The control muscles are described as "negative." Pressure, circulatory disturbances and inactivity were felt to be responsible for the changes in the muscles. Voegt suggested that degenerating muscle may liberate thrombogenic substances leading to terminal thrombosis.

In 1938 Neumann³ reported his observations on a series of 165 consecutive autopsies in which the venous system was widely and thoroughly searched for thrombi. Special attention was paid to the veins of the lower extremities, and the report is based mainly on these findings. The series included autopsies on 84 females and 81 males, aged 17 to 88 years. In the 100 subjects showing thrombosis of the lower extremities the localization was: plantar region, 71 per cent; internal malleolar region, 17 per cent; leg, 87 per cent, and thigh, 22 per cent. Never was thrombosis limited to the thigh. Neumann attached great importance to the fact that the malleolar vessels, connecting the feet and legs, were so seldom involved even when both the plantar and the leg vessels contained thrombi. This seems to be the basis for his conclusion that there must be two centers of origin for venous clotting in the lower extremities, namely, the plantar and the leg region. The veins of the calf were much more often affected alone (29 per cent) than were the plantar veins (12 per cent). Also the more frequent combinations of occluded veins, leaving out of consideration the malleolar canal vessels, placed the veins of the calf far ahead of all others. The most common combination proved to be bilateral involvement of the veins of the calf and the foot. Neumann postulated two clinical types of thrombosis, based on the site of origin: (1) a benign variety, starting in the veins of the legs and characterized by slow progression of the clots, increasing in frequency with age and having a tendency toward multiple but non-fatal pulmonary embolism; (2) a malignant form, centered in the plantar region and typified by rapidly progressing thrombosis occurring in younger people, not rising in frequency with age and tending toward fulminating, fatal embolism of the lungs. He expressed the belief that the source of emboli for both types is a thrombus that has progressed into the veins of the thigh. In progressive ascending thrombosis, segmentation of the clots results at over-crossings by ligaments, tendons and similar structures, and under these thrombi are usually lacking. Much stress is laid on flat feet, as a cause both of plantar thrombosis and of its localization to the vena plantaris lateralis. Persons with normal or

high arches usually had occlusion of all plantar veins rather than of the vena plantaris lateralis alone.

Two venous over-crossings, designated "proximal plantar venous point" and "distal plantar venous point" are believed by Neumann to be of importance with respect to segmentation of thrombi in the lateral plantar veins, since these points can be projected on the sole of the foot by a special method and are therefore clinically significant for the timely recognition of malignant plantar venous thrombosis. The proximal point is easily found, because it lies under the internal malleolus close to the calcaneus. The distal one is mapped out by measuring the greatest breadth of the sole over the heel and again over the ball of the foot, drawing a line through the midpoint of each and connecting the lines by a third. The highest point of the internal malleolus and the median tubercle of the first metatarsal bone are next connected by a line, and at the midpoint of this another line is drawn perpendicularly across the sole until it bisects the one previously made on the plantar aspect. Where these intersect is the "distal venous point." The accuracy of this observation was checked anatomically by inserting needles and dissecting along their course. The vena plantaris lateralis was never missed by more than 2 mm. Payr⁹ and Tschmarke¹⁰ have described pressure pain over the proximal plantar venous point as a delicate sign of incipient thrombosis of the foot, and Neumann has expressed the belief that the sign appears still earlier at his distal point. Olow¹¹ has said that in venous thrombosis of the calf pain can be elicited at the junction of the gastrocnemius muscle and the achilles tendon, and Krieg¹² asserted that pain on pressure over the distal end of the adductor canal is an indication of thrombosis of the veins of the thigh.

Of Neumann's subjects with thrombosis of the lower extremities, 11.8 per cent had fulminating fatal pulmonary embolism, and more than 80 per cent of these exhibited clots in the veins of the feet and calves. If the cases of nonfatal multiple pulmonary emboli are included, the lower extremities account for 52.8 per cent of the clots lodging in the lungs. Neumann's strong conviction that the so-called "malignant" type of thrombosis, centered in the plantar veins, occurs at an earlier age than

9. Payr, E.: Gedanken und Beobachtungen über die Thrombo-Emboliefrage. Anregung zu einer Sammelforschung, Zentralbl. f. Chir. **57**:961, 1930; cited by Neumann.³

10. Tschmarke, G.: Erfahrungen über den Fuss-sohlendruckschmerz als Frühsymptom der Thrombose, Chirurg **3**:924, 1931; abstracted, München. med. Wchnschr. **78**:2135, 1931; cited by Neumann.³

11. Olow, J.: Sur un detail concernant le diagnostic de la thrombose crurale, Acta obst. et gynec. Scandinav. **10**:159, 1930, cited by Neumann.³

12. Krieg, E.: Zum klinischen Bild der infektiösen Fernthrombose, München. med. Wchnschr. **82**:776, 1935; cited by Neumann.³

involvement of the veins of the calf appears to be based on the fact that the 3 youngest persons of his series, all under 20 years of age, harbored such thrombi. However, reference to the text and to his table 2 shows that plantar thrombosis varies but little among the different age groups.

For reasons mentioned earlier we were seldom able to dissect the veins of the whole lower extremity. In the small number of patients who could thus be studied, occlusion of the plantar veins was observed only once. Fifteen surgically amputated legs were available for critical study; again only 1 instance of thrombosis was found in the sole of the foot. Admittedly our observations are too few to allow for any conclusions, but as far as they go are not in accord with Neumann's findings.

Neumann, in common with many others, has laid great emphasis on the frequent absence of thrombi in the veins of the thigh in cases of pulmonary embolism, even though the veins of the calf are full of antemortem clots. Neumann traced only 18 per cent of fulminating embolism to the veins of the leg. Both he, and Rössle,² supported the empiric observation that massive embolic exodus from leg veins rarely results fatally. It is generally admitted that venous thrombi tend to propagate toward the heart, placing the newest part of the clot proximally. We concur with the latter observation. If this is true, is it not both possible and probable that the primary seat of thrombosis is the calf or even the foot and that there would be no thrombosis of the femoral veins if clotting did not first take place peripherally? True, it may be the propagated portions that become massive and fatal emboli, but have physicians not heretofore paid altogether too much attention to the larger and more apparent clots and forgotten the real source of the trouble? The matter is of more than academic interest, for if anything is to be done to prevent the initial clotting it is most important that attention be focused on the primary seat and action not delayed until extension into large veins has had time to take place.

Belt¹³ in answer to a query as to whether the "leg veins" listed in his splendid study¹⁴ meant those of the calf, stated that his explorations were largely confined to the femoral and saphenous veins, from which the emboli seemed to come, and added significantly: "I have always felt the thrombosis was not primary in these vessels but began in the smaller vessels of the lower leg."

The most recent thorough investigation is that of Frykholm.⁴ The veins of the muscles of the calf were involved in 39 cases; clots occurred in the posterior tibial and peroneal veins 25 times; the veins of the

13. Belt, T. H.: Personal communication to the authors, 1939.

14. Belt, T. H.: Thrombosis and Pulmonary Embolism, *Am. J. Path.* **10**: 129, 1934.

adductor muscles of the thigh were thrombosed in 16 cases and in 9 others the deep femoral vein was simultaneously blocked; the pelvic veins were implicated only 8 times. The gross observations were amply supplemented by microscopic studies. Frykholm also dissected the veins of the gluteal region, the extensor musculature of the lower extremities and the anterior tibial veins. The results were negative. Only 2 dissections of the plantar veins are recorded; 1 revealed a thrombus in the posterior tibial vein posterior to the malleolus. There were 24 instances of pulmonary embolism, but the author failed to state which of the possible sources appeared to be responsible. Always progression of the thrombotic process was in the direction of the blood stream; retrograde extension was a rarity. It is Frykholm's concept that during confinement to bed the thin walls of the veins collapse from mechanical pressure, allowing intima to contact intima, especially in the adductor muscles and the muscles of the calf, which take the least part in active movement while a person is in bed and through which minimal amounts of blood pass. Since normal metabolism of the intima depends on its contact with the circulating blood, collapse may easily disturb the nutrition of the endothelium and in this way become an important primary condition leading to thrombosis by giving off substances from the damaged endothelium which promote coagulation of blood. He conceived that it is also possible for the plantar and the pelvic veins to collapse under certain circumstances, with like results.

PROPHYLAXIS AND TREATMENT

From our own study and from the writings of others, it would appear that there is no one cause for thrombosis of the veins of the leg. Although it would be short sighted not to admit that a number of factors may operate, we are strongly of the opinion that the major role is played by forced recumbency of adult persons who prior to an illness or operation have been active or at least ambulatory. Then, all too frequently, these people are put to bed for varying periods of time and allowed to lie quietly, without recognition of the simple physiologic principle that gravity and muscular activity are of major importance in the efficient return of venous blood from the extremities. Or, worse still, pillows are supplied for the comfort of the patient and the already anatomically existent "bottle neck" at the popliteal vein is enhanced, or the hospital bed is broken at the middle and the same bad situation is produced.

Many authors have stressed the value of exercise in bed and the importance of early rising with respect to thrombus prevention, so we make no claim to originality in asserting our firm belief that a fundamental therapeutic procedure, unless there are definite contraindications,

is the prescription of periodic, active flexion and extension of the feet, legs and thighs, frequent turning of helpless patients, prevention or relief of abdominal distention, and deep breathing exercises throughout the period of rest in bed. Orders for these measures should be written on the hospital chart by the physician, who should then see to it that the nurses are carrying out his instructions. It is well to have the patient demonstrate to the physician so that any alterations or corrections can be made. This serves well as a check on the nurse in charge. Since the sensation of scraping of the toes against the sheet is unpleasant, better cooperation will be obtained by loosening the bedding or by having the patient lie on his side while exercising. Some patients prefer to have something solid to push against and will do better by being allowed to slide down until the feet contact the end of the bed. The variable resistance bicycle pedal device recently described by de Takáts and Jesser¹⁵ would appear ideal for such a purpose. Homans¹⁶ recommended elevation of the foot of the bed, which will enable gravity to aid the return of venous blood. Frykholm⁴ raised the head of the bed, necessitating movement of the patient to overcome the sensation of sliding downward.

Active motion is vastly superior to passive movement or massage. The latter is definitely contraindicated unless it is started immediately after confinement. Our observation of several instances of thrombus formation within three days after a patient's going to bed leads us to believe that even active movement cannot be employed with impunity unless it is instituted soon after the beginning of recumbency. If exercise is delayed for even a few days, there is at least potential danger of dislodging portions of fresh thrombi. A patient already ill for a few days before a physician is consulted had best be allowed to remain quiet.

While determination of the prothrombin content of the blood will aid in detecting persons who are likely to have thrombosis, it is not readily done routinely. The use of heparin to inhibit clotting has likewise been suggested for the prevention of thrombosis, but the cost will make its use limited. On the other hand, exercise costs nothing beyond a little additional work for the nursing staff, and the principle of using it is sound, not only physiologically but psychologically, since the patient's mind is kept occupied and muscle tone is maintained.

While the emphasis should be on prevention, some means of treatment must be at hand for patients in whom small emboli have demon-

15. de Takáts, G., and Jesser, J. H.: Pulmonary Embolism, *J. A. M. A.* **114**: 1415 (April 13) 1940.

16. Homans, J.: Varieties of Thrombophlebitis of the Limbs: Their Origin, Course and Treatment, *Am. J. Surg.* **44**:3, 1939.

strated their presence. Homans¹⁶ advised ligation of the femoral vein under such circumstances.

SUMMARY

Thrombosis of the deep veins of the leg is appallingly frequent among middle-aged and older persons forced to bed for varying periods of time. The incidence in the present study was 52.7 per cent.

Bilateral involvement was found 110 times and unilateral 75 times. The right side alone was affected a little more often than was the left. Thrombi formed in the veins accompanying the larger arteries far more frequently than in other veins and were present in the soleus muscle more often than in the gastrocnemius.

Fatal pulmonary embolism was responsible for 3.13 per cent of all deaths; in 45.4 per cent of the cases of death from such embolism the most probable source was thrombosed leg veins. There is good authority for the belief that although fulminating emboli often spring from the femoral vessels, thrombosis here represents an extension from older clots in the legs and feet. From the standpoint of prophylaxis and treatment, recognition of this is most important.

Lesser emboli frequently originate from the veins of the calf. Showers of these, even though of small diameter, may consist of long clots, which, by buckling or coiling, are capable of occluding even the major pulmonary arteries. Repeated embolic episodes are more frequent than a single massive attack. Multiple small fragments can also do harm, by placing an added burden on an already embarrassed circulatory system.

In the present series there was little difference in the incidence of thrombosis between medical and surgical patients or between males and females.

Phlebitis, either as a cause or as a complication of thrombosis, had a minor role in our cases.

As a rule, phlebothrombosis of the deep veins of the leg is clinically silent and for this reason is likely to be forgotten until embolic phenomena appear.

We are of the opinion that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person without the benefit of active exercise or the aid of gravity in the maintenance of an efficient venous circulation.

Planned and supervised voluntary movement and the elimination of too much comfort for the legs should do much to reduce incidence of thrombosis and its all too frequent sequel—pulmonary embolism.

SERUM LIPIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND IN PATIENTS WITH OBSTRUCTIVE JAUNDICE

A COMPARATIVE STUDY

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In 1933 Hench¹ reported the analgesic effect of jaundice in cases of chronic arthritis, fibrositis and sciatic pain and followed this report with several papers on further observations of the phenomenon. Sidel and Abrams,² Borman,³ and others have confirmed these observations. Hench stated that bilirubin appears to be the most likely agent responsible for the beneficial effect of jaundice on arthritis. This appears true in view of Race's findings⁴ that the icteric index and the concentration of serum bilirubin are likely to be low among patients who have rheumatoid arthritis. However, Hench suggested the possibility that bile salts, hepatic autolysate, special diet or other factors may be responsible

From the Rackham Arthritis Research Unit, the Medical School, University of Michigan. The Rackham Arthritis Research Unit is supported by the Horace H. Rackham School of Graduate Studies.

1. Hench, P. S.: Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis and Sciatic Pain, *Proc. Staff Meet., Mayo Clin.* **8**:430-436 (July 12) 1933; Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, *J. A. M. A.* **101**:1265-1266 (Oct. 14) 1933; The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, *Ann. Int. Med.* **7**:1278-1294 (April) 1934; A Clinic on Some Diseases of Joints: IV. The Inactivation of Chronic Infectious Arthritis and Fibrositis by Jaundice, *M. Clin. North America* **19**:573-583 (Sept.) 1935; Effect of Jaundice on Chronic Infectious (Atrophic) Arthritis and on Primary Fibrositis: Further Observations; Attempts to Reproduce the Phenomenon, *Arch. Int. Med.* **61**:451-480 (March) 1938.

2. Sidel, N., and Abrams, M. I.: Jaundice in Arthritis: Its Analgesic Action, *New England J. Med.* **210**:181-182 (Jan. 25) 1934.

3. Borman, M. C.: Jaundice in Arthritis, with Report of Two Cases, *Wisconsin M. J.* **35**:890-891 (Nov.) 1936.

4. Race, J.: *Biochemical Investigation in Chronic Rheumatic Diseases: Report on Chronic Rheumatic Diseases*, London, H. K. Lewis & Co., Ltd., 1935, no. 1, pp. 55-71.

for the phenomenon. Assuming that the responsible agent ("factor X") is a specific chemical substance or a combination of substances and not a nonspecific set of circumstances, Hench further speculated that this phenomenon results from (a) the correction of some chemical deficiency, (b) the correction of some chemical oversufficiency or (c) a process of bacteriolysis, bacteriostasis or detoxification.

Hench attempted to produce therapeutic jaundice by administering bilirubin, bile salts, synthetic bile salts, diluted ox bile, human bile and liver extracts and by transfusions of blood from highly jaundiced persons, with disappointing results. Wolff,⁵ McGowan^{6a} and McGowan, Bollman and Mann^{6b} suggested the use of toluylenediamine to produce artificial jaundice, but Hench¹ found this type of jaundice to be ineffective against arthritic pain. Thompson and Wyatt⁷ observed that the bilirubin level in the serum of patients with arthritis averaged 1.39 mg. per hundred cubic centimeters, as compared with the average of 2.06 mg. in normal persons. They were able to induce nontoxic jaundice by the injection of bilirubin dissolved in sodium carbonate plus a solution of the sodium salt of dehydrocholic acid, and this jaundice had an ameliorating effect on the symptoms of rheumatoid arthritis; the administration of either bile salts or bilirubin alone did not produce jaundice, nor was there any clinical benefit therefrom.

Most attempts to isolate this "factor X" in jaundice which produces relief from arthritis have been made with the idea that bilirubin, bile salts or bile acids are responsible. In our study attention has been turned to other abnormal constituents of the blood in persons with jaundice, the lipids. A comparative study of the lipid partition of serum was made on patients with obstructive jaundice, on patients with rheumatoid arthritis and on normal subjects for the following reasons: (1) to establish the existence or absence of any abnormality in the serum lipid values of persons with arthritis; (2) to compare the serum lipids in patients with arthritis with those present in persons with obstructive jaundice, and (3) to determine whether changes in serum lipids associated with obstructive jaundice could be the basis for the beneficial effect of jaundice on rheumatoid arthritis.

5. Wolff, H. J.: The Physiologic Action of Toluylenediamine and Its Relation to Experimental Jaundice, *J. Pharmacol. & Exper. Therap.* **50**:407-419 (April) 1934.

6. (a) McGowan, J. M.: Bile Salts in Toluylenediamine Jaundice, *Proc. Staff Meet., Mayo Clin.* **10**:565-567 (Sept. 4) 1935. (b) McGowan, J. M.; Bollman, J. L., and Mann, F. C.: The Bile Acids in Icterus Produced by Toluylenediamine, *J. Pharmacol. & Exper. Therap.* **58**:305-311 (Nov.) 1936.

7. Thompson, H. E., and Wyatt, B. L.: Experimentally Induced Jaundice (Hyperbilirubinemia): Report of Animal Experimentation and of the Physiologic Effect of Jaundice in Patients with Atrophic Arthritis, *Arch. Int. Med.* **61**:481-500 (March) 1938.

PROCEDURE

Subjects.—Studies were made on 12 patients with arthritis. Eleven of these had typical rheumatoid arthritis; 7 were men and 4 were women. Their ages varied from 29 to 56; the duration of disease ranged from four months to twenty years. One patient (L. D.) with spondylitis rhizomelica was studied; he was 28 years of age, and the disease had existed for six years at the time of this study.

Serum Values in Normal Subjects, in Patients with Arthritis and in Patients with Obstructive Jaundice

Subject	Age	Sex	Duration of Dis- ease, Mo.	Days on Diet	Total Lipid, Mg. per 100 Cc.	Phos- pho- lipid, Mg. per 100 Cc.	Iodine	Cholesterol				
								Total, Mg. per 100 Cc.	Free, Mg. per 100 Cc.	Ester, Mg. per 100 Cc.	Ester	Bili- rubin, Mg. per 100 Cc.
											Total Choles- terol, Per- cent- age	
Patient with rheumatoid arthritis												
R. J.	51	M	240	0	624	208	67	183	45	138	75.4	...
M. R.	56	F	72	0	794	227	63	140	44	96	68.6	...
M. K.	30	M	18	0	926	267	66	243	53	190	78.2	...
L. D.	28	M	72	0	471	242	74	127	36	91	71.7	...
C. M.	46	F	90	0	399	222	70	112	31	72	64.3	...
D. L.	45	F	36	7	566	170	80	189	44	145	76.7	...
F. S.	53	M	24	7	610	218	61	156	43	113	72.4	...
H. G.	42	M	60	7	447	...	77	165	38	127	77.0	...
R. S.	35	M	24	7	545	311	68	134	33	101	75.4	...
G. C.	55	F	36	0	545	295	73	214	58	156	72.9	...
K. N.	29	M	96	7	498	217	61	139	39	100	71.9	...
S. G.	52	M	4	7	583	425	65	124	33	91	73.4	...
Average.....	584	255	69	161	41	118	73.2	
Patients with jaundice												
R. S.	55	M	..	0	1,108	586	56	130	80	50	38.5	9.0
E. L.	38	F	..	0	2,026	1,093	59	330	151	179	54.2	5.0
S. S.	70	F	..	0	598	347	70	204	52	152	74.5	5.8
G. S.	52	M	..	0	1,580	941	46	313	264	49	15.7	16.0
H. K.	59	M	..	0	2,166	1,016	50	422	290	132	31.3	4.6
Average.....	1,496	797	56	280	167	112	42.8	8.1
Normal controls												
R. A.	23	F	..	7	559	177	66	97	29	68	70.1	
M. D.	22	F	..	7	510	157	60	162	38	124	76.5	
A. C.	28	F	..	7	553	...	85	195	58	137	70.3	
R. F.	35	M	..	0	610	226	73	210	47	153	72.9	
Average.....	558	187	71	163	43	121	72.5	

Five patients with obstructive jaundice were studied; 3 were men and 2 were women; their ages varied from 38 to 70. Three of these patients (R. S., E. L. and S. S.) suffered from biliary obstruction due to carcinoma of the head of the pancreas. One patient (G. S.) had cirrhosis of the liver, and another (H. K.) had obstructive jaundice due to gallstones in the common bile duct.

Four normal subjects were studied as controls; 3 were women whose ages varied from 22 to 28, and 1 was a 35 year old man.

Preparation of Subjects.—All samples of blood were taken from subjects after a twelve hour fasting period. Whenever possible, identical diets of approximately 2,400 calories per day were fed for seven days preceding the venipuncture. This

diet consisted of 80 Gm. of protein, 175 Gm. of carbohydrate and 150 Gm. of fat. Six of the 12 patients with arthritis and 3 of the 4 controls were fed this diet (table 1). Because of gastrointestinal difficulties it was impossible for the jaundiced patients to eat this diet.

Chemical Methods.—Fifty to 60 cc. of blood was taken, allowed to clot and centrifuged. Twenty-five cubic centimeters of serum was then extracted by the ether-alcohol procedure of Bloor,⁸ evaporated to dryness in vacuo, dissolved in purified petroleum benzine U. S. P. (petroleum ether) and made up to a volume of 100 cc. Aliquots of this stock solution were used in the determinations. Gravimetric determinations of total lipids were carried out in duplicate. Phospholipid determinations were made in triplicate by an adaptation to the Evelyn photoelectric colorimeter of the Fiske-Subbarow aminonaphthol-sulfonic acid-phosphate method⁹ after precipitation of the phospholipids with acetone according to the method of Bloor.¹⁰ Total and free cholesterol were determined in triplicate analyses by an adaptation to the photoelectric colorimeter of the Schoenheimer-Sperry method¹¹ of precipitation with digitonin, and ester cholesterol values were calculated by difference. The iodine value was determined by the pyridine sulfate dibromide method of Rosenmund and Kuhnhehn,¹² and the bilirubin concentration was measured by the van den Bergh method.¹³

RESULTS

Results of all the analyses appear in the table. The total lipid values for the group of patients with arthritis varied from 399 to 926 mg. per hundred cubic centimeters, with an average of 584 mg., as compared with 558 mg. for the control group. The iodine values averaged 69 for the former and 71 for the latter. Analyses for serum phospholipids in the former group gave an average of 255 mg. per hundred cubic centimeters, in contrast to an average of 187 mg. in the latter group. Average values of 161, 41 and 118 mg. per hundred cubic centimeters were found for total, free and ester cholesterol, respectively, in the group of patients with arthritis, while the control group had average values of 166, 43 and 121 mg. The percentage of cholesterol present in the ester form was essentially the same in the two groups, as shown by the averages of 73.2 for the patients with arthritis and 72.5 for the controls.

In the group of patients with jaundice the total serum lipids varied from 598 to 2,166 mg. per hundred cubic centimeters, with an average

8. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, *J. Biol. Chem.* **77**:55-73 (April) 1928.

9. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375-400 (Dec.) 1925.

10. Bloor, W. R.: The Oxidative Determination of Phospholipid (Lecithin and Cephalin) in Blood and Tissues, *J. Biol. Chem.* **82**:273-286 (May) 1929.

11. Schoenheimer, R., and Sperry, W. M.: A Micro Method for the Determination of Free and Combined Cholesterol, *J. Biol. Chem.* **106**:745-760 (Sept.) 1934.

12. Rosenmund, K. W., and Kuhnhehn, W.: Eine neue Methode zur Jodzählbestimmung in Fetten und Ölen unter Verwendung von Pyridinsulfardibromid, *Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel* **46**:154-159, 1923.

13. van den Bergh, A. A. H.: *Der Gallenfarbstoff in Blute*, Leiden, 1918.

value of 1,496. The iodine value averaged 56.2, and the levels of serum phospholipid averaged 797 mg. per hundred cubic centimeters. The average values for total, free and ester cholesterol were 280, 167 and 112 mg. per hundred cubic centimeters, respectively. The average percentage of esterified cholesterol was 42.8.

COMMENT

Previous studies on the lipid fractions of the blood in rheumatoid arthritis have led to contradictory results. Kauftheil¹⁴ found high cholesterol values during severe inflammation in cases of rheumatoid arthritis and normal values when the inflammation subsided. Bruger¹⁵ and his co-workers reported a decrease in total cholesterol with a normal relationship between the free and ester fractions, while Gorham and Meyers¹⁶ and Pemberton and Foster¹⁷ found normal values for total cholesterol in patients with arthritis. Our results show similar values for total, free and ester cholesterol in the group of patients with arthritis and in the control group, and likewise the percentage of esterified cholesterol is nearly identical in the two groups, which confirms the results of the latter workers.

In 4 of the 5 patients with jaundice, the total values for serum lipids were extremely high, and in all patients the serum phospholipids were increased to values two to three times those of the normal subjects. White, Deutsch and Maddock¹⁸ found similar increases in phospholipids

14. Kauftheil, L.: Ueber den Cholesteringehalt des Blutserums bei Gelenkerkrankungen, *Wien. Arch. f. inn. Med.* **19**:273-284 (Nov.) 1929.

15. (a) Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteoarthritis and Arteriosclerosis), *Arch. Int. Med.* **53**:422-434 (March) 1934. (b) Hartung, E. F.; Greene, C. H., and Bruger, M.: Calcium and Cholesterol Metabolism in Arthritis, *Proc. Am. A. Study & Control Rheumat. Dis.*, 1934, p. 14. (c) Hartung, E. F., and Bruger, M.: The Cholesterol Content of the Plasma in Arthritis, *J. Lab. & Clin. Med.* **20**:675-681 (April) 1935.

16. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, *Arch. Int. Med.* **20**:599-612 (Oct.) 1917.

17. (a) Pemberton, R.: Arthritis and Rheumatoid Conditions, ed. 2, Philadelphia, Lea & Febiger, 1935. (b) Pemberton, R., and Foster, G. L.: Studies on Arthritis in the Army Based on Four Hundred Cases: III. Studies on the Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, *Arch. Int. Med.* **25**:243-282 (March) 1920.

18. White, F. W.; Deutsch, E., and Maddock, S.: (a) The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester, and Phospholipid Tests in Diseases of the Liver: I. The Results of the Tests, *Am. J. Digest. Dis.* **6**:603-610 (Nov.) 1939; (b) II. A Clinical Comparison of the Tests, *ibid.* **6**:3-7 (Jan.) 1940.

in 90 per cent of their patients with obstructive jaundice, and Chanutin and Ludewig¹⁹ observed an increase in the plasma phosphatide phosphorus in rats with ligated bile ducts.

The total cholesterol values were above normal in 4 of our 5 patients with jaundice, and free cholesterol was high in all, the average value being four times the normal level. The hypercholesteremia observed in these patients with obstructive jaundice is in agreement with the results obtained in man by Epstein,²⁰ Wilkinson²¹ and White, Deutsch and Maddock,¹⁸ in dogs by Hawkins and Wright²² and in rats by Chanutin and Ludewig.¹⁹ The latter workers also found a direct proportionality between the free cholesterol and the phospholipid phosphorus, while our results only roughly show such a proportionality.

Our findings indicate that the ester cholesterol was below normal in 2 cases and above normal in 3 while in 4 cases the failure of the ester cholesterol to parallel the increase in the free cholesterol resulted in a lowered cholesterol-ester ratio. Epstein²⁰ reported similarly varying ratios; in half of his cases of obstructive jaundice the esters rose proportionately with the free cholesterol; in other cases the ester fraction did not rise sufficiently to maintain the normal ratios, and in 8 of 43 cases there was a fall in cholesterol esters. White, Deutsch and Maddock¹⁸ found that in 80 per cent of their patients the cholesterol ester values were below their normal value of 60 per cent of the total cholesterol. Chanutin and Ludewig¹⁹ reported that the plasma cholesterol esters in rats with ligated bile ducts were normal or slightly above normal, but that the rise in free cholesterol resulted in a lowered ratio of ester cholesterol to total cholesterol.

No correlation could be found between the bilirubin levels and the total serum lipids or any lipid fraction. One patient with jaundice (S. S.) had normal values for total serum lipids and cholesterol, but the level of serum phospholipid was high.

19. Chanutin, A., and Ludewig, S.: The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct, *J. Biol. Chem.* **115**:1-7 (Aug.) 1936.

20. (a) Epstein, E. Z.: The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, *Arch. Int. Med.* **47**:82-93 (Jan.) 1931; (b) Cholesterol of the Blood Plasma in Hepatic and Biliary Disease, *ibid.* **50**: 203-222 (Aug.) 1932. (c) Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Disease, *ibid.* **58**:860-890 (Nov.) 1936.

21. Wilkinson, S. A.: Cholesterol Metabolism in Jaundice, *Am. J. Digest. Dis. & Nutrition* **3**:618-622 (Nov.) 1936.

22. Hawkins, W. B., and Wright, A.: Blood Plasma Cholesterol Fluctuations Due to Liver Injury and Bile Duct Obstruction, *J. Exper. Med.* **59**:427-439 (April) 1934.

There were no definite abnormalities in the total serum lipids or in any of its fractions in patients with arthritis. The therapeutic results secured by jaundice might lead to the premise that these results are due to elevation of serum lipids such as that obtained during obstructive jaundice. However, if this assumption is correct one might expect a low level of serum lipids in persons with arthritis, in contrast to the high level of serum lipids in patients with jaundice, so that the jaundice might act as though correcting a deficiency state. However, no such opposite values for serum lipids were found, and such a mechanism for the beneficial results of jaundice cannot be concluded. However, the extremely high values for phospholipids and for total and free cholesterol observed in persons with jaundice may be a factor in the phenomenon of the analgesic effect of jaundice.

SUMMARY

In patients with arthritis the ratio of ester cholesterol to total cholesterol was normal. The values for total, free and ester serum cholesterol were found to be nearly identical with the values in normal control subjects. Normal values for total serum lipids were obtained from persons with arthritis, whereas levels of serum phospholipids were slightly elevated.

In patients with obstructive jaundice, the levels of total serum lipids and serum phospholipids were extremely high, the levels of total and free cholesterol were markedly increased over normal levels and the percentage of cholesterol combined in the ester form was far below that found in normal subjects.

The serum lipids in patients with arthritis are not below normal; hence jaundice is not beneficial to arthritic patients by reason of correcting a lipid deficiency, but it is possible that the extremely high levels of total lipids, phospholipids and total and free cholesterol which are present in jaundice may be a factor in causing the beneficial effect of jaundice on arthritis.

IMMEDIATE SERUM REACTIONS IN MAN
CLASSIFICATION AND ANALYSIS OF REACTIONS TO INTRAVENOUS
ADMINISTRATION OF ANTIPNEUMOCOCCUS HORSE SERUM
IN CASES OF PNEUMONIA

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Since Jan. 1, 1937 reports on the use of concentrated antipneumococcus serum have been submitted on a uniform record to the New York State Department of Health by physicians employing serums produced or purchased and distributed by the Division of Laboratories and Research.¹ The questions on that form are concerned, so far as possible, with objective data, so that the effect of interpretation by the reporting physician is minimized. Through a follow-up system, complete reports were obtained in practically every case.²

Early study of the material so collected brought to light a number of immediate reactions following intravenous serum therapy which were associated with severe circulatory collapse and which did not seem to be related to protein hypersensitivity in the usual sense. It was recognized that this impression was based on reports which had the disadvantage of containing second hand information of varying degrees of accuracy. In order to obtain further information regarding such reactions, the literature was reviewed and a study undertaken.

A review of the literature on serum reaction disclosed many reports of the occurrence of death during the administration of serum, which

From the Bureau of Pneumonia Control, New York State Department of Health.

This study received financial aid in part from the Metropolitan Life Insurance Company and in part from the Commonwealth Fund.

1. Physicians and hospitals throughout the state of New York cooperated in this study.

2. Rogers, E. S.; Rutstein, D. D., and others: Study of Antipneumococcus Horse Serum in the Treatment of More than Five Thousand Cases, to be published.

are well summarized for all types of serum therapy up to 1930³ and for the serum treatment of pneumonia up to 1939.⁴ Additional reports have been made since that time.⁵ Studies have been published presenting the relationship to reactions of previous injections of serum,⁶ positive cutaneous reactions,⁷ the amount of serum injected⁸ and the concentration of the serum.⁹ Most of these studies failed to differentiate between immediate serum reactions and the delayed reaction, or "serum sickness."¹⁰ There were also expositions regarding the nature of serum

3. (a) Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substances, *J. A. M. A.* **82**:1091-1098 (April 5) 1924. (b) Bullowa, J. G. M., and Jacobi, M.: Fatal Human Anaphylactic Shock: Report of a Case, with Autopsy Observations and Review of the Literature, *Arch. Int. Med.* **46**:306 (Aug.) 1930.

4. Heffron, R.: Pneumonia with Special Reference to Pneumococcus Lobar Pneumonia, New York, The Commonwealth Fund, 1939, p. 863.

5. (a) Waldbott, G. L.: Prevention of Anaphylactic Shock with Study of Nine Fatal Cases, *J. A. M. A.* **98**:446-449 (Feb. 6) 1932; (b) Allergic Death: Protracted Shock, *Arch. Int. Med.* **54**:597-605 (Oct.) 1934. (c) Tuft, L.: Fatalities Following Reinjection of Foreign Serum: Report of Unusual Case, *Am. J. M. Sc.* **175**:325-331 (March) 1928. (d) Freedman, H. J.: Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum: Report of Fatal Case, *New England J. Med.* **212**:10 (Jan. 3) 1935.

6. (a) Lyall, H. W., and Murdick, P. P.: Tetanus Antitoxin: Serum Reactions Following Prophylactic Injection, *New York State J. Med.* **38**:882-885 (June 1) 1938. (b) Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, *J. Immunol.* **9**:7-16 (Jan.) 1924. (c) Park, W. H.: Human Hypersensitiveness to Whole Serum or Serum Globulins Following Diphtheria Toxin Antitoxin Injections: Its Importance, *ibid.* **9**:17-24 (Jan.) 1924. (d) Bauer, E. L., and Wilmer, H. B.: Toxin Antitoxin: Hypersensitivity to Its Protein Content, *J. A. M. A.* **86**:942 (March 27) 1926. (e) Spicer, S.: Effect of Previous Administration of Antitoxin and Toxin Antitoxin on Serum Reaction, *ibid.* **90**:1778-1779 (June 2) 1928.

7. Davis, H. M.: Horse Serum Skin Tests, *J. Hyg.* **38**:325-330 (May) 1938. Clairborn, L. N.: Ophthalmic Test for Sensitivity to Horse Serum, *J. A. M. A.* **98**:1718-1720 (May 14) 1932. Spicer, S.: Ophthalmic Test for Horse Serum Sensitivity Contrasted with Intradermal, Performed on Three Hundred and Fifty-Three Patients, *J. Immunol.* **15**:335-342 (July) 1928. Lyall and Murdick.^{6a}

8. (a) Gerlough, T. D.: Relation of Incidence of Serum Disease to Square Root of Amount of Antiserum Injected, *J. Infect. Dis.* **56**:317-320 (May-June) 1935. (b) Hunt, L. W.: Recent Observations in Serum Disease, *J. A. M. A.* **99**:909-912 (Sept. 10) 1932.

9. Park, W. H., and Throne, B.: The Results of the Use of Refined Diphtheria Antitoxin, Gibson's "Globulin Preparation," in the Treatment of Diphtheria, *Am. J. M. Sc.* **132**:686 (Dec.) 1906. Rosenau, M. J., and Anderson, J. F.: Studies upon Hypersusceptibility and Immunity, *Hygienic Laboratory Bulletin* 36, United States Treasury Department, Public Health Service, 1907. Weaver, G. N.: Serum Disease, *Arch. Int. Med.* **3**:485 (Aug.) 1909. Lyall and Murdick.^{6a} Hunt.^{8b}

10. von Pirquet, C. F., and Schick, B.: *Die Serumkrankheit*, Leipzig, Franz Deuticke, 1905.

reactions in man,¹¹ the interpretation of the mechanism of which usually was based on the results of animal experimentation.

The enormous literature on reactions in animals will not be reviewed here, as excellent summaries are available.¹² One of the outstanding facts evident in that literature is the wide variation in the response to the injection of foreign proteins, depending on the species of animal used.¹³ Such differences emphasize the need for greater caution in attempting to interpret the symptoms occurring during serum reactions in man on the basis of experiments performed on other animal species.

No report was found of serum treatment of human subjects in which a tabulation, a classification and an analysis of all immediate reactions were presented. This lack of data probably is inherent in the fact that the relative infrequency of such reactions in the experience of any one physician or hospital precludes the possibility of a comprehensive study.

In order to increase the accuracy of the reports which indicated the occurrence of immediate serum reactions, a personal visit was made to the majority of physicians reporting such reactions during the period from Jan. 1 to Oct. 1, 1938. Also included in this investigation were reports indicating a history of allergy, a positive cutaneous or ophthalmic test with horse serum or death within eight hours of the administration

11. (a) Mackenzie, G. M., and Hanger, F. M.: Serum Disease and Serum Accidents, *J. A. M. A.* **94**:260-265 (Jan. 25) 1930. (b) Rackemann, F. M.: *Clinical Allergy*, New York, The Macmillan Company, 1931. (c) Rudolph, J. A., and Cohen, M. B.: Types of Human Hypersensitiveness: Their Relationship to Liability to Serum Reactions, *J. A. M. A.* **102**:900 (March 24) 1934. (d) Seegal, B. C., in Gay, F. P., and others: *Agents of Disease and Host Resistance*, Springfield, Ill., Charles C. Thomas, Publisher, 1935, chap. 6, p. 36.

12. Wells, H. G.: Present Status of Problems of Anaphylaxis, *Physiol. Rev.* **1**:44 (Jan.) 1921. Karsner, H. T., in Jordan, E. O., and Falk, I. S.: *Newer Knowledge of Bacteriology and Immunology*, Chicago, University of Chicago Press, 1928, chap. 73, p. 966. Topley, W. W. C., and Wilson, G. S.: *The Principles of Bacteriology and Immunology*, Baltimore, William Wood & Company, 1936, p. 889. Zinsser, H.; Enders, J. F., and Fothergill, L. D.: *Immunity: Principles and Application in Medicine and Public Health*, New York, The Macmillan Company, 1939, p. 349. Seegal.^{11d}

13. Auer, J., and Lewis, P. A.: Acute Anaphylactic Death in Guinea-Pigs: Its Cause and Possible Prevention; a Preliminary Note, *J. A. M. A.* **53**:458 (Aug. 7) 1909; Physiology of the Immediate Reaction of Anaphylaxis in the Guinea-Pig, *J. Exper. Med.* **12**:151 (April) 1910. Weil, R.: Liver in Shock and Peptone Poisoning, *J. Immunol.* **2**:525 (Oct.) 1917. Coca, A. F.: Mechanism of Anaphylaxis Reaction in Rabbit, *ibid.* **4**:219 (Oct.) 1919. Edmunds, C. W.: Anaphylaxis in the Cat and Opossum, *J. Pharmacol. & Exper. Therap.* **5**:518 (May) 1914. Parker, J. T., and Parker, F., Jr.: Anaphylaxis in White Rat, *J. M. Research* **44**:263 (March) 1924. Ritz, H.: Ueber Antikörperbildung und Anaphylaxie bei weissen Mäusen, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **9**:321 (Aug.) 1911. Kopeloff, N.; Davidoff, L. M., and Kopeloff, L. M.: General and Cerebral Anaphylaxis in Monkey, *J. Immunol.* **30**:477 (June) 1936.

of serum, even if no reaction occurred. During the interview with the reporting physician, confirmatory and supplementary information was requested and was recorded on a special study form. The hospital record was examined in every case in which hospitalization had occurred, and any other medically trained observers of the reaction, such as interns and nurses, were interviewed. This study also included reactions which were personally observed in patients in the pneumonia service of the Albany Hospital.

For the purpose of the study, an immediate reaction was defined as any untoward change in the patient's condition which was reported as occurring during injection of serum or within two hours of the time injection was started. Serum sickness after that interval was excluded, as it rarely endangers the life of the patient.¹⁴ All gradations of immediate reaction were included, from one spot of urticaria, slight dyspnea or chilly sensations to fatal reactions. No selection of cases for investigation was made.

During the period from Jan. 1 to Oct. 1, 1938, 535 cases out of about 800 reported during that period were investigated according to the aforementioned plan. Of these 535 cases, reactions were found to have occurred in 449. Although this group of investigated cases is included in the larger group of 790 cases in which immediate reactions were reported and which are analyzed in this paper, separate analyses of these two groups led to the same conclusions.

CLASSIFICATION OF REACTIONS

A study of the characteristics of the reactions encountered suggested a logical division into four classes: thermal, anaphylactic, circulatory and miscellaneous. Definitions of these reactions and reports of cases illustrating their clinical picture follow.

Thermal Reaction.—This class included every reaction characterized by chilly sensations or a shaking chill with or without a subsequent rise in temperature and every one with a sudden rise in temperature without a recognizable chill (infrequent) occurring during or shortly after the administration of serum.

Typical case histories exemplifying mild and severe thermal reactions follow:

M. L., an 11 year old white girl, had the onset of pneumonia Feb. 11, 1938. She was hospitalized on February 12. Pneumococcus type I was found in the sputum. The personal history was not remarkable, and there was no history of

14. Clark, E., and Kaplan, B. I.: Endocardial Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. **24**:458-475 (Oct.) 1937. Clark, E.: Serum Carditis: Morphologic Cardiac Alterations in Man Associated with Serum Disease, J. A. M. A. **110**:1098-1100 (April 2) 1938.

allergy. The patient had never received horse serum previously. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was negative. The ophthalmic reaction to 0.1 cc. (1:10 dilution) horse serum was negative. Administration of serum was begun on February 12, at 2 a. m., when the patient was given 20 cc. of type I antipneumococcus horse serum (lot 42B) diluted with 50 cc. of physiologic solution of sodium chloride over a period of one-half hour; there was no reaction. At 10 a. m. on that day a similar injection of the same amount of type I antipneumococcus horse serum of the same lot number, diluted in the same amount of physiologic solution of sodium chloride, was administered over a period of one-half hour. At the end of the injection the patient coughed and had a moderate shaking chill. The pulse was rapid and was of fair quality. There was no asthma or urticaria. The temperature, which had been 103.2 F., rose to 105.8 F. by 10:45 a. m. The pulse and the respiratory rates remained relatively unchanged. The reaction was followed by an immediate crisis. On February 16 the patient had a severe bout of serum sickness consisting of arthritis, urticaria and lymphadenitis, which persisted for four days. Recovery was then uneventful.

H. Q., a 64 year old man, had the onset of pneumonia March 1, 1938. He was hospitalized on March 7, on which date *Pneumococcus* type VIII was found in the sputum. The personal history was not remarkable, and there was no history of allergy. It was not known whether serum had been administered previously. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was negative. Administration of serum was begun at 4:45 p. m. on March 7, when 40 cc. of type VIII antipneumococcus serum (lot 8-05A) in 250 cc. of physiologic solution of sodium chloride was injected intravenously over a period of fifteen minutes. One hour and five minutes later the patient had a severe chill followed by an elevation of temperature from 103.2 to 108 F., of pulse rate from 88 to 146 and of respiratory rate from 24 to 40. He became delirious. The pulse volume remained good throughout the reaction. There was no vascular collapse, asthma or urticaria. The patient received treatment for the symptoms and gradually recovered.

At 10:30 p. m. on the same day 40 cc. of the same lot of serum diluted with 250 cc. of physiologic solution of sodium chloride was administered over a period of one-half hour. Thirty-five minutes after the injection was completed a reaction occurred which was similar to the first one, but not so severe. The temperature rose from 102 to 102.4 F. and the respiratory rate from 22 to 32. The pulse remained unchanged. After the second injection the patient had an immediate crisis. There was no serum sickness, and recovery from pneumonia was uneventful.

Anaphylactic Reaction.—This type of reaction was characterized by the occurrence of any combination of the following symptoms: itching, urticaria, asthma, angioneurotic edema and laryngeal edema. Reactions presenting these symptoms with or without circulatory changes were included in this class.

Case histories exemplifying the mild and the severe form of this type of reaction follow:

G. P., a 12 year old white boy, had the onset of pneumonia May 23, 1938. He was hospitalized on May 25. *Pneumococcus* type I was found in the sputum. The personal history was not remarkable except that the patient had received tetanus antitoxin in November 1930; there was no history of allergy. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was an increase in the size of the wheal with development of pseudopodia and a surrounding area of erythema.

Administration of type I antipneumococcus horse serum was begun on May 27. The data are included in the accompanying tabulation.

Dose	Date	Lot No.	Time Started	Time Completed	Amount of Serum	Amount of Physiologic Solution of Sodium Chloride	Reaction
1	5/27	1 - 50A	12:25 a.m.	12:26 a.m.	0.1 cc.	0	None
2	5/27	1 - 50A	12:45 a.m.	12:50 a.m.	1.0 cc.	0	None
3	5/27	1 - 50A	1:05 a.m.	1:25 a.m.	9.0 cc.	125 cc.	Present

By the time the third injection was completed, flushing of the face had developed, which change was followed by generalized urticaria and itching. Relief was obtained with 0.3 cc. of epinephrine hydrochloride administered subcutaneously. At 1:35 a. m. the patient vomited once and then received 0.7 cc. of epinephrine hydrochloride subcutaneously. The reaction gradually abated, and the patient had completely recovered by 2 a. m.

Administration of serum was then resumed, as follows:

Dose	Date	Lot No.	Time Started	Time Completed	Amount of Serum	Amount of Physiologic Solution of Sodium Chloride	Reaction
4	5/27	1 - 47B	11:00 a.m.	11:30 a.m.	8 cc.	500 cc.	None
5	5/27	1 - 47B	11:13 p.m.	11:25 p.m.	30 cc.	200 cc.	Present

At the end of the fifth injection, the patient complained of itching of the extensor surfaces of the extremities. There were urticarial wheals in this area, which disappeared spontaneously after some minutes. Recovery from pneumonia was uneventful.

M. N., a 5 year old white girl, had the onset of pneumonia May 15, 1938. She was hospitalized May 16. Pneumococcus type I was found in the sputum. The personal history was not remarkable except for the occurrence of purpura two months previously, at which time 3 per cent of eosinophils were found in smears of the peripheral blood. Otherwise there was no history of allergy. There had been no previous administration of serum. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was a slight increase in the size of the wheal, which was surrounded by an area of erythema 3 cm. in diameter.

Administration of serum was begun at 10 p. m. on May 17, when 0.2 cc. of type I antipneumococcus horse serum (lot 1-50A) was mixed with 2 cc. of physiologic solution of sodium chloride and slowly injected. When the injection was about one-half completed, at 10:01 p. m., the patient complained of itching of the nose and toes, after which complaint she sneezed; then generalized urticaria and marked circumoral pallor developed. The pulse was weak, thready and rapid, although the exact rate was not determined. The rhythm of the pulse was occasionally irregular. The patient felt cold and clammy. There was considerable dyspnea, with a prolonged expiratory phase to the respirations, and the chest was filled with sibilant and sonorous rales. The patient was given 3 minims (0.18 cc.) of epinephrine hydrochloride, and her recovery was complete about one-half hour later.

No further serum therapy was attempted. There was no serum sickness.

Circulatory Reaction.—Any reaction characterized by the occurrence of sudden circulatory changes, such as a rapid, thready or irregular pulse, asystole, "shock," "vascular collapse" (which is sometimes asso-

ciated with coma), profuse cold perspiration, constrictive chest pain, a drop in blood pressure or sudden death, was included in this class, provided that none of the symptoms characterizing the anaphylactic reaction were present. The reactions of all patients with asthmatic symptoms occurring during an immediate reaction were classified as anaphylactic even though in a few instances it seemed fairly evident that this symptom was based on cardiac disease and was the result of acute failure of the left ventricle.¹⁵

The following records are typical of the mild and the severe form of this type of reaction.

J. C., a 69 year old white man, was seen by his physician six hours after the onset of his disease, on April 15, 1938. Pneumococcus type VIII was found in the sputum. The patient had known of his hypertension for eight to ten years, but had been without symptoms of cardiac disturbance. There was no history of allergy. The patient had never received serum therapy. The cutaneous reaction to 0.1 cc. (1:10 dilution) of horse serum was negative. Administration of serum was begun at 11 p. m. on April 15, when an injection of 40 cc. of type VIII anti-pneumococcus horse serum (lots 8-04A and 8-05A) was given, at the rate of 1 cc. per minute. During administration of the last 2 cc. of the dose the patient became cyanotic and the pulse was more rapid and felt irregular, weak and thready. Slight dyspnea was also present. There was no urticaria, asthma or chill, and the reaction was not unduly alarming. Ten minims (0.61 cc.) of epinephrine hydrochloride was given, with immediate relief. The patient had an immediate crisis, and no further serum was administered. There was no serum sickness.

D. V., a 58 year old white woman, had the onset of pneumonia May 27, 1938. She was hospitalized May 27. Pneumococcus type V was obtained from the sputum on June 3. There was no history of allergy. It was not known whether the patient had ever received serum previously. There was "myocardial weakness," with moderate dyspnea on exertion. The ophthalmic reaction to 0.1 cc. (1:10 dilution) of horse serum was negative.

Administration of serum was begun on June 3, when 40 cc. of type V anti-pneumococcus horse serum (lot 357H88J) was injected intravenously, at the rate of about 1 cc. per minute. Near the end of the injection the patient became restless, after which change she suddenly stopped breathing and involuntarily urinated and defecated. It was noted that the patient had become pulseless, and it was thought she had died. One cubic centimeter of epinephrine hydrochloride was given intramuscularly immediately, and the patient responded relatively rapidly. When she became conscious she complained of severe pain in the back. At this time the pulse was weak and thready and there was marked dyspnea, but no asthmatic breathing. The entire reaction was over in about ten minutes. Neither urticaria nor chill was associated with this reaction.

The patient did not have serum sickness, and her recovery from pneumonia was uneventful.

15. Krehl, L.: *Die Erkrankungen des Herzmuskels und die nervösen Herzkrankheiten*, Vienna, 1901, pp. 116-120; cited by Pratt, J. H.: *Cardiac Asthma*, J. A. M. A. **87**:809 (Sept. 11) 1926. Palmer, R. S., and White, P. D.: *Clinical Significance of Cardiac Asthma: Review of Two Hundred and Fifty Cases*, *ibid.* **92**:431-434 (Feb. 9) 1929.

Miscellaneous Reactions.—This class included the reactions which were characterized by a variety of minor symptoms but which could not be placed in any of the first three classes. The character and incidence of the various symptoms encountered are listed in table 1. It is possible that further knowledge will permit reallocation of some of the reactions from this heterogeneous class to one of the other classes.

As in most biologic classifications, there were borderline cases, but for the most part the reactions observed fitted easily into the classes described. In this paper, each of the four types, that is, the thermal reaction, the anaphylactic reaction, the circulatory reaction and the mis-

TABLE 1.—*Character and Frequency of Symptoms Encountered in Patients with Miscellaneous Reactions*

Grouped Symptoms	Frequency
Respiratory..... (Including dyspnea, cyanosis, choking, change in rate or rhythm of respirations; excluding asthmatic breathing)	62
Precordial..... (Including pain in precordial region, tightness in chest, substernal pain or pressure; excluding the circulatory reaction)	18
Pulse rate..... (Including increase or decrease in rate; excluding changes in excursion or rhythm of pulse)	22
Skeletal..... (Pain in lumbar region of back or in extremities, muscular rigidity)	20
Abdominal..... (Nausea, vomiting, abdominal pain, desire to defecate)	20
Cerebral..... (Headache, coma, dizziness, faintness, throbbing of head, blurring of vision)	22
Cutaneous..... (Including flushing, sensation of heat, perspiration, pallor; excluding urticaria or itching)	15
Total frequency of grouped symptoms.....	188*

* These grouped symptoms were observed 188 times in 116 patients presenting only a reaction classified here.

cellaneous reactions, was considered a potential component of any given immediate serum reaction. Some patients were encountered whose reactions presented one component on one injection and a different component on one of the following injections. Occasionally a reaction presented several components on a single injection, for example, the occurrence of urticaria (anaphylactic component) during the serum injection and a chill (thermal component) an hour later.

In table 2, the character and frequency of simple reactions, those consisting of only one component, are contrasted with the character and frequency of combined reactions, those consisting of two or more components. The occurrence of different components in the reaction to the same injection or to successive injections given the same patient is considered a combined reaction.

ANALYSIS OF THE DATA

A total of 2,340¹⁶ cases of types I, II, V, VII and VIII pneumococcic pneumonia in which the patients were treated with concentrated type-specific horse serum by intravenous injection were reported from Jan. 1 to Dec. 31, 1938. Immediate serum reactions were observed in 790, or 33.8 per cent, of these cases. The remaining 1,550 cases, in which reactions did not occur, may be considered as a control group. As the definition of an immediate reaction varies widely, it is difficult to compare the total incidence of reactions in this study with that in other published reports.¹⁷

TABLE 2.—*Distribution of Reactions According to Components Encountered in Individual Patients*

Reaction	Number of Patients	Percentage of Total Number of Patients
Thermal	218	27.6
Anaphylactic	130	16.4
Circulatory	67	8.5
Miscellaneous	116	14.7
Simple	531	67.2
Thermal and anaphylactic	50	6.3
Thermal and circulatory	55	7.0
Thermal and miscellaneous	92	11.7
Anaphylactic and circulatory	3	0.4
Anaphylactic and miscellaneous	16	2.0
Circulatory and miscellaneous	12	1.5
Thermal, anaphylactic and circulatory	3	0.4
Thermal, anaphylactic and miscellaneous	9	1.1
Thermal, circulatory and miscellaneous	4	0.5
Anaphylactic, circulatory and miscellaneous.....
Thermal, anaphylactic, circulatory and miscellaneous.....
Combined	244	30.9
Reaction not described	15	1.9
Total number of reactions...	790	100.0

The frequency of immediate reactions varied widely with the type of antipneumococcus serum employed (table 3), being highest with type VIII serum (70.2 per cent) and lowest with type I serum (24.3 per cent).

16. This does not include 12 cases in which the details of serum treatment are unknown.

17. (a) Bullowa, J. G. M.: *The Management of the Pneumonias*, New York, Oxford University Press, 1937. (b) Finland, M., and Brown, J. W.: *Specific Treatment of Pneumococcus Type I Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide*, *Am. J. M. Sc.* **197**:151-168 (Feb.) 1939. (c) Brown, J. W., and Finland, M.: *Specific Treatment of Pneumococcus Type II Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide*, *ibid.* **197**:369-380 (March) 1939. (d) Finland, M., and Brown, J. W.: *Specific Treatment of Pneumococcus Type V and Type VII Pneumonias, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide*, *ibid.* **197**:381-393 (March) 1939. (e) Heffron.⁴

The incidence of reactions in each age group (table 4) was uniform, with the exception of a slightly diminished frequency during the first decade of life, an observation which indicated that age has little effect.

Dilution of serum with physiologic solution of sodium chloride did not appreciably decrease the occurrence of reactions (table 5). Dilution under 1:1 resulted in a somewhat diminished incidence, which, however, was not statistically significant.

TABLE 3.—*Incidence of Immediate Reactions According to Type of Specific Antipneumococcus Serum Given*

Type of Serum Given	Total Number of Patients	Patients with Reaction	Percentage with Reaction
I.....	1,383	336	24.3
II.....	231	116	50.2
V.....	270	69	25.6
VII.....	251	125	49.8
VIII.....	205	144	70.2
Total.....	2,340	790	33.8

TABLE 4.—*Incidence of Immediate Reactions According to Age*

Age Group	Total Number of Patients	Patients with Reaction	Percentage with Reaction
Under 10.....	289	65	22.5
10 to 19.....	313	116	37.1
20 to 39.....	660	227	34.4
40 to 59.....	716	252	35.2
60 and over.....	359	129	35.9
Unknown.....	3	1
All ages.....	2,340	790	33.8

TABLE 5.—*Frequency of Immediate Reactions According to Dilution of Serum with Physiologic Solution of Sodium Chloride*

Ratio of Solution to Serum	Total Number of Patients	Patients with Reaction	Percentage with Reaction
None.....	518	199	38.4
Under 1: 1.....	145	41	28.3
1: 1 to 3: 1.....	226	83	36.7
3: 1 and over.....	745	258	34.6
"Fixed" dilution*.....	1,634	581	35.6
"Variable" dilution.....	706	209	29.6
Total number of patients.....	2,340	790	33.8

* "Fixed" dilution refers to a constant ratio of solution of sodium chloride to serum in all injections in the treatment of the same patient, in contrast to "variable" dilution, which refers to an inconstant ratio.

ANALYSIS OF REACTIONS IN TERMS OF COMPONENTS

The overlapping of components in some reactions necessitated analysis of the reactions in terms of the total number of components observed. Therefore, the total number of reaction components was greater than the total number of patients in whom the reactions occurred.

The incidence of reaction components tended to vary according to the type of antipneumococcus serum employed (table 6).

Thermal reactions occurred most frequently with the type VIII serum (56.7 per cent) and least often with type V serum (8.5 per cent), although wide variations were noted in the frequency of reactions with any given type, depending on the lot of serum employed. Heffron,⁴ in summarizing the literature on the incidence of thermal reactions fol-

TABLE 6.—*Frequency of Reaction Components According to Type of Specific Serum Injected Intravenously*

Reaction Components	Frequency of Reaction Components						Percentage of Components Among Total Number of Patients Receiving Each Specific Type						Total
	I	II	V	VII	VIII	Total	I	II	V	VII	VIII		
Thermal.....	155	71	23	65	116	431	11.2	20.7	8.5	26.3	56.7	18.4	
Anaphylactic...	103	38	20	25	15	211	7.4	16.5	11.1	10.0	7.3	9.0	
Circulatory.....	51	18	12	31	32	144	3.7	7.8	4.4	12.4	15.6	6.2	
Miscellaneous...	105	24	23	49	38	259	7.7	14.7	8.5	19.5	18.5	10.7	
Total no. of patients	1,353	231	270	251	205	2,340							

TABLE 7.—*Frequency of Reaction Components According to Age*

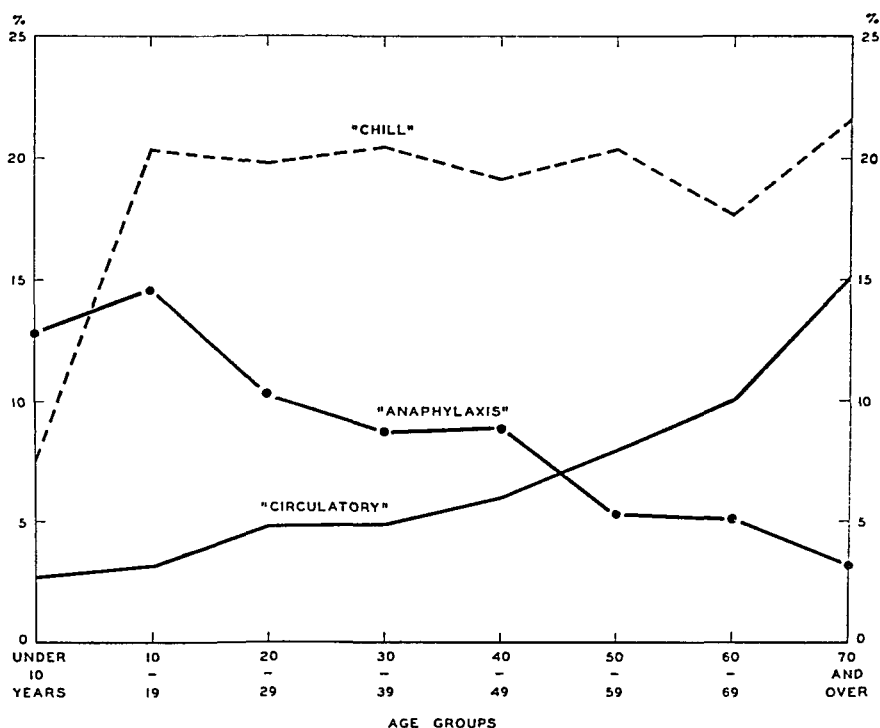
Age Groups	Frequency of Reaction Components				Total Number of Patients	Percentage of Total Number of Patients in Each Age Group According to Reaction Components			
	Thermal	Anaphylactic	Circulatory	Miscellaneous		Thermal	Anaphylactic	Circulatory	Miscellaneous
Under 10.....	22	35	8	13	259	7.6	12.8	2.7	4.5
10 to 19.....	64	46	10	24	313	20.4	14.6	3.2	7.6
20 to 29.....	54	25	13	32	273	19.8	10.3	4.8	11.7
30 to 39.....	80	34	19	45	387	20.5	8.7	4.9	11.5
40 to 49.....	73	34	23	47	379	19.2	9.0	6.0	12.3
50 to 59.....	63	18	27	47	337	20.4	5.3	8.0	13.9
60 to 69.....	42	12	24	24	235	17.7	5.1	10.1	10.1
70 and over.....	27	4	19	18	124	21.6	3.2	15.2	14.4
Age unknown.....	1	..	3
All ages.....	431	211	144	259	2,340	18.4	9.0	6.2	10.7

lowing the use of concentrated antipneumococcus horse serum, indicated that such reactions may occur in 10 to 20 per cent of adult patients. The total incidence of thermal reactions in this series was 18.4 per cent.

Anaphylactic reactions occurred in 9 per cent of all cases. It was not possible to compare this incidence with figures given in the literature because of differences in definition. The occurrence of anaphylactic reactions among the patients in this series varied less from type to type than did that of thermal reactions. The low incidence of anaphylactic reactions in cases of type VIII pneumococcic pneumonia may have depended to some extent on the older age distribution in these cases as compared with that in cases of other types of infection (table 7).²

Circulatory reactions were encountered in 6.2 per cent of all the cases (table 6). The high incidence of this type of reaction in cases of type VIII pneumococcic pneumonia (15.6 per cent) also may have depended on the age distribution.

There were striking differences in the age-incidence relations of the various components, as shown in table 7 and the chart. The incidence of thermal reactions in each age group was remarkably constant except that for patients under 10 years of age. The incidence of anaphylactic reactions, on the other hand, decreased as the age of the patients increased. In marked contrast, the incidence of circulatory



Incidence of reaction components among patients in each age group who were treated with intravenous injections of specific antipneumococcus horse serum (types I, II, V, VII and VIII).

reactions took the opposite trend, since the frequency of this type of reaction increases directly with age. The almost perfect uniformity of these two trends in reverse directions was highly significant.

The incidence of a history of allergy (15.5 per cent) and of positive cutaneous reactions (20.2 per cent) among patients having anaphylactic reactions was lower than expected (tables 8 and 9). However, compared with the rates for patients with thermal and circulatory reactions, the frequency of a history of allergy or of positive cutaneous reactions among patients having anaphylactic reactions was approximately twice

as great. If one were to assume that the circulatory reaction represented a degree of protein hypersensitiveness so extreme as to cause a type of reaction in which the circulatory symptoms overshadowed those of asthma and urticaria, one might expect an incidence of positive cutaneous reactions and a history of allergy at least as great as that among those less sensitive patients in whom the reaction was mild enough to allow the symptoms of asthma and urticaria to appear. On

TABLE 8.—*Frequency of Positive History of Allergy According to Reaction Components and Incidence of Reactions*

Reaction Components *	Record of History of Allergy	Positive History of Allergy	Percentage Positive of Recorded Histories
Thermal.....	368	32	8.7
Anaphylactic.....	174	27	15.5
Circulatory.....	112	8	7.1
Miscellaneous.....	197	19	9.6
Total number of patients with reaction....	647	64	9.9
Total number of patients without reaction	1,424	71	5.0
Total number of patients.....	2,071	135	6.5

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.

TABLE 9.—*Frequency of Positive Cutaneous Reactions According to Reaction Components and Incidence of Reactions*

Reaction of Components *	Record of Cutaneous Test	Positive Cutaneous Reactions	Percentage Positive of Recorded Cutaneous Reactions
Thermal.....	412	35	8.5
Anaphylactic.....	203	41	20.2
Circulatory.....	136	13	9.5
Miscellaneous.....	235	28	11.9
Total number of patients with reaction....	749	87	11.6
Total number of patients without reaction	1,443	67	4.7
Total number of patients.....	2,192	154	7.0

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.

the contrary, the frequency of a history of allergy or of positive cutaneous reactions among patients having circulatory reactions was of the same order as the frequency among those having thermal reactions, the nature of which generally has been felt not to be on the basis of protein hypersensitivity.¹⁸

The total number of positive ophthalmic reactions (in 13 of a total of 1,399 tests known to have been performed) was so small as to make

18. (a) Sabin, A. B., and Wallace, G. B.: On Nature of Chill-Producing Principle in Antipneumococcus Serum, J. Exper. Med. **53**:339-362 (March) 1931.
(b) Heffron.⁴

it impossible to determine the significance of the test in a series of patients treated with serum but unavoidably selected so as to remove the more sensitive persons prior to therapy.

An immediate reaction followed the intravenous injection of a test dose of 1 to 2 cc. in only 3 per cent of 366 patients on whom it was known that the test was performed. In spite of this fact, an immediate reaction to at least one of the therapeutic injections following the test dose occurred in 57 per cent of these same patients. Although the arterial blood pressure and pulse rate were not closely observed by the attending physician during injection of most of these test doses, it was the experience at the Albany Hospital, where such observations were made, that the intravenous injection of a test dose was of little value in

TABLE 10.—*Frequency of Preexisting Cardiovascular Disease According to Reaction Components and Incidence of Reactions*

Reaction Components *	Record of Preexisting Complications	Preexisting Cardiovascular Disease †	Percentage of Preexisting Cardiovascular Disease in Recorded Preexisting Complications
Thermal.....	390	36	9.2
Anaphylactic.....	192	13	6.8
Circulatory.....	130	24	18.5
Other.....	232	22	9.5
Total number of patients with reaction....	720	71	9.9
Total number of patients without reaction	1,399	90	6.4
Total number of patients.....	2,119	161	7.6

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.
† Exclusive of uncomplicated arteriosclerosis.

predicting the occurrence of an immediate serum reaction to a therapeutic dose.

The incidence of circulatory reactions was approximately twice as great as that of thermal reactions and three times as great as that of anaphylactic reactions among patients with a history of preexisting cardiovascular disease, exclusive of uncomplicated arteriosclerosis (table 10). This observation integrates easily with the age distributions of each of the reaction components as previously noted.

The fatality rates of the patients with and of those without reactions were practically the same (table 11).

In relation to the individual reaction components, the fatality rate among those patients having thermal reactions (11.4 per cent) was only two thirds of the rate among patients without reactions (16.4 per cent). This difference was independent of the age factor, since the incidence of thermal reactions was uniform for all age groups, as indicated in table 7. However, the greater frequency of bacteremia among the patients with-

out reaction (19.9 per cent of 607 patients for whom cultures of the blood were made) than among the patients in whom thermal reactions (12.0 per cent of 183 patients) occurred made it impossible to attach any significance to this difference. Heffron and Robinson¹⁹ also found no significant difference in their series of cases of type I pneumococcic pneumonia.

The low fatality rate of the patients having an anaphylactic reaction (10.9 per cent) was most likely related to the high proportion of young persons among those in whom this type of reaction occurred (table 7).

As indicated previously, patients with circulatory reactions had a strikingly high fatality rate (31.9 per cent), twice as high as the patients without such reactions. This was to be expected because of the older age distribution of patients with this type of reaction (table 7), because some of these reactions were fatal in themselves (table 12) and,

TABLE 11.—*Outcome of Pneumonia According to Reaction Components and Incidence of Reactions*

Reaction Components *	Lived	Died	Total	Fatality Rate (Percentage)
Thermal.....	382	49	431	11.4
Anaphylactic.....	188	23	211	10.9
Circulatory.....	98	46	144	31.9
Miscellaneous.....	212	37	249 †	14.9
Total number of patients with reaction.....	668	121	789 †	15.3
Total number of patients without reaction..	1,296	254	1,550	16.4
Total number of patients.....	1,964	375	2,339 †	16.0

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.

† Exclusive of 1 patient in whose case the outcome is unknown.

finally, because this group of patients presented the highest incidence of preexisting cardiovascular disease (table 10).

A comparison of the varying degrees of dilution in relation to individual reaction components yielded results similar to those observed in the entire group of patients having immediate reactions (table 5). Dilution was not found to have any effect on the rate of occurrence of any of the reaction components.

The sex of the patient receiving the serum was not a factor in the occurrence of all the immediate reactions or of the individual reaction components. There were approximately 65 per cent males and 35 per cent females in each of the groups comprising the total number of patients, the patients with reactions and the individual reaction components.

The problem of sensitization due to previous injections of serum was not clarified by the evidence at hand, since the majority of patients

19. Heffron, R., and Robinson, E. S.: Final Report of Massachusetts Pneumonia Study and Service 1931-1935, Commonwealth 24:2 (Jan.-March) 1937.

TABLE 12.—Data Concerning Patients Whose Deaths During 1937,

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
1937	1	I	22 F	Pregnancy, 7 mo.; miscarriage during pneumonia	None	None	Unknown	Negative	Poor	28A	None
	2	I	75 F	"Cardiac"	None	None	Negative	Negative	Unknown	Unknown	None
	3	I	67 F	Unknown	Negative	Unknown	Negative	Not done	Fair	Unknown	None
	4	I	30 F	Pregnancy, 7 mo.	None	None	Negative	Negative	(?) Poor	40B	1 cc. (N. R.)†
	5	II	80 F	Unknown	None	None	Negative	Not done	Unknown	9B	None
	6	II	53 M	Generalized arteriosclerosis	None	None	Negative	Negative	Unknown	Unknown	None
1938	7	I	62 M	Syphilis of central nervous system; intrinsic asthma, 3 yr.	Eczema and hives in past	None	Negative	Negative	Fair	38B	1 cc. (N. R.)
	8	I	42 F	Obesity; "myocarditis"	None	None	Negative	Not done	Fair	1-45A 1-45B	1 cc. (N. R.)
	9	I	55 M	None	Asthma, 3 to 4 yr.	None	Negative	Negative	Poor	1-47B	1 cc. (N. R.)
	10	II	82 M	Hypertension; cerebral hemorrhage 6 mo. previously	None	None	Negative	Not done	Poor	2-18A	5 minims (N. R.)

* Ratio of serum to physiologic solution of sodium chloride. † In this table N. R. indicates no reaction.

1938 and 1939 Were "Definitely" Due to Administration of Serum

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
10	10	1	1:1	30 min.	Sudden rapid, weak and thready pulse, becoming imperceptible associated with rapid respiration, at end of injection	None	Acute reaction followed by pulmonary edema and death after 25 min.
40	40	1	1:4	1 hr. 30 min.	Sudden dilatation of pupils; deep cyanosis; rapid and weak pulse; shallow breathing at end of serum administration	None	Artificial respiration and epinephrine hydrochloride necessary to revive patient; condition much worse after reaction, remaining poor until death
80	20	4	Unknown	15 to 20 min.	"Acute cardiac failure"; sudden vascular collapse with no asthma or urticaria	None	Patient moribund on admission, but noticeably improved on morning of fatal injection; no reaction to previous injections
20	19	1	Unknown	1 hr.	Sudden increased cyanosis, associated with weak and irregular pulse; no asthma or urticaria	None	Data somewhat conflicting as to details; death unquestionably related to serum
192	24	4	1:7	30 min.	Sudden circulatory collapse; respiratory standstill and death; no asthma or urticaria	Lobar pneumonia in upper, middle and lower lobes of right lung; congestion and cloudy swelling of viscera	No response to epinephrine hydrochloride; no reaction to previous injections
120	48	2	1:4	7 min.	Sudden circulatory collapse at end of injection with increased cyanosis and dyspnea	Lobar pneumonia in right lung; fibrinous pericarditis; hypertrophy and dilatation of heart; cloudy swelling of liver	
36	35	1	1:5	End of injection	Sudden onset of coughing, dyspnea, asthma and cyanosis	Extreme congestion of blood vessels in kidney; lobar pneumonia; congestion and edema at base of lungs	
100	20	7	1:5	About 3 hr.	Onset of nausea, cloudy vision, cyanosis and dyspnea during injection; pulse rapid and thready; condition poor for 3 hr.; sudden convulsive seizure, followed by death; no asthma or urticaria	Lobar pneumonia in upper lobe of right lung; both lower lobes collapsed; "toxic myocarditis"	No reactions to previous injections
120	20	4	0	End of injection	Color suddenly ashen; two gasps, no pulse, no heart sounds; no response to intracardiac injection of epinephrine hydrochloride	"No cause for sudden death found," only pneumonia and pyoarthritis in left elbow observed	No reactions to previous injections
5	5	1	0	During injection	Sudden collapse without complaint; color ashen; skin clammy; pulse not palpable; no asthma or urticaria	None	Physician's belief, heart stopped before respirations

TABLE 12.—Data Concerning Patients Whose Deaths During 1937, 1938

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
	11	II	67 M	"Chronic myocarditis"	None	None	Negative	Negative	Fair	2-21A	1 cc. (N. R.)
	12	II	27 F	Mild hyperthyroidism	None	Diphtheria antitoxin, 17 yr. previously	Negative	Negative	Good	2-13A 2-23B	None
	13	VII	52 M	"Severe cardiac"; had had attacks of decompensation; pneumonia occurred during an attack	None	Unknown	Negative	Negative	Poor	7-06	None
	14	VII	39 F	None	Unknown	Unknown	Not done	Negative	Poor	7-06	4 cc. (N. R.)
	15	VII	68 F	"Chronic myocarditis"	None	None	Negative	Negative	Good	7-06	None
	16	VIII	23 M	Rheumatic heart disease with mitral stenosis and regurgitation	None	None	Negative	Negative	Good	2B	1 cc. (N. R.)
	17	VIII	44 F	Extreme depression due to death in family	None	None	Negative	Negative	Poor	2B	1 cc. (N. R.)
	18	VIII	53 M	None	None	None	Negative	Negative	Good	2B	1 cc. (N. R.)

and 1939 Were "Definitely" Due to Administration of Serum—Continued

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injec- tions	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
40	40	1	1:10	2 hr. 45 min.	Chills, cyanosis with labored respirations, considerable dyspnea during injection; deepening of cyanosis; pulse rapid and irregular; failure of patient to rally despite intensive treatment with epinephrine hydrochloride, caffeine, 25 per cent solution of pyridine betacarboxylic acid diethylamide (coramine) and oxygen	None	Onset of reaction half-way through projected injection of 75 cc.; injection stopped when about 40 cc. given
55	7	2	1:4	End of injection	Sudden pain in right side of chest associated with peripheral collapse and extreme cyanosis; no asthma or urticaria	None	First dose of 48 cc. given without reaction; patient improving from pneumonia at time fatal dose given; some question whether second dose was necessary
40	40	1	1:12	End of injection	Sudden desire to defecate; death of patient while being placed on bed pan with needle still in vein; no pulse, no heart sound; no asthma or urticaria	None	Complication of cardiac disease and increase of blood volume by injection of 540 cc. of fluid in 40 min.; serum responsible for death according to physician who administered it
70	40	3	0	6 min.	Increase in cyanosis followed by cessation of pulse; respirations rapid; death of patient within 1 min. after onset of reaction	None	Severe pain in back following second dose, only previous reaction
100	40	3	0	20 hr.	Severe dyspnea, almost imperceptible pulse and severe chill at end of injection; temperature rise from 101.8 to 103.2 F.; patient irrational; no recovery from reaction; continuation of weak and thready pulse; no asthma or urticaria	None	Severe lumbar pain, cyanosis, nausea and vomiting after second injection; rise in pulse from 100 to 120; rapid recovery from this reaction, although next injection fatal; no reaction to first dose
40	20	2	1:8	2 hr. 40 min.	Few hives around site of injection at end of injection; no further symptoms until 20 min. later; severe chill followed by rapid respiration, air hunger, rapid and thready pulse, pulmonary edema; course persistently downhill	None	"Patient appeared to die a cardiac death"; no reaction from first injection
40	39	1	0	1 hr. 20 min.	Slight chill followed by circulatory collapse with rapid and thready pulse one hour after injection; death within 20 min.; no asthma or urticaria	None	Patient uncooperative because of mental depression since death of mother 3 wk. previously
40	39	1	0	1 hr. 15 min.	Chill, cyanosis, panting respirations, apprehensiveness, restlessness, stupor, rapid pulse and increasing pulmonary edema 35 min. after injection; condition unchanged for 15 min.; sudden death; no asthma or urticaria	None	Patient in excellent clinical condition; disease mild; reasonable doubt whether serum advisable because of mildness of symptoms

TABLE 12.—Data Concerning Patients Whose Deaths During 1937, 1938

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Chemical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
	19	VIII	75 M	None	None	None	Negative	Not done	Good	S 04	1 cc (N R)
	20	VIII	78 M	Hypertension; arteriosclerotic heart disease with auricular fibrillation	None	None	Negative	Not done	Poor	S 04	None
	21	VIII	81 M	Arteriosclerotic heart disease	None	None	Negative	Negative	Poor	S 04	2 cc (N R)
	22	VI	63 M	Hypertension; cerebral accident, June 1938	None	Unknown	Negative	Negative	Poor	6 01	1 cc (N R)
	23	IV	73 F	Arteriosclerotic heart disease	None	None	Negative	Negative	Poor	4 02	1 cc (N R)
1939	24	II	79 M	"Myocarditis"	Unknown	Unknown	Unknown	Unknown	Unknown	2 25	1 to 2 cc. (fatal)
	25	V	44 F	Rheumatic heart disease with mitral stenosis and insufficiency 6 mo pregnant; miscarriage, day before onset of pneumonia with retained fragments and severe postpartum bleeding; red blood cells 1,000,000 on admission	Hay fever as a child; none as an adult	None	Negative	Negative	Poor	5 11A	1 cc. (N R)

and 1939 Were "Definitely" Due to Administration of Serum—Concluded

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
36	35	1	0	2½ days	Appearance of poor color, rapid and thready pulse, dyspnea and cold and clammy feeling during injection; survived for 2½ days, in poor condition; no recovery from reaction; no asthma or urticaria	None	Physician's belief, serum direct cause of death; pneumonia mild
35	35	1	0	20 min.	Restlessness, suffocation, collapse and death during injection; no asthma or urticaria	None	Physician's belief, death due to an acute cardiac episode
90	40	5	1:4	8 hr.	Sudden collapse with rapid and thready pulse, irregular respirations and coma at end of injection; condition relatively unchanged for 6 hr.; then pulmonary edema and death; no asthma or urticaria	None	Slight chill with labored respirations after second injection; no other reactions
100	99	1	1:1	End of injection	Sudden abdominal pain, rapid, thready and weak pulse and cold and clammy feeling during injection of last few cubic centimeters; pulse increasingly irregular; death within few minutes; no asthma or urticaria	Lobar pneumonia; extreme coronary sclerosis with multiple tiny old healed myocardial infarcts	
100	99	1	1:3	15 min.	Cries because of pain in chest shortly after end of injection; pulse weak and thready; collapse and death in 15 min.; no asthma or urticaria	Lobar pneumonia in middle and lower lobes of right lung; fibrinous pericarditis; anomalous origin of coronary arteries; atheroma of aorta	"Final episode clinically coronary occlusion, coronary spasm or pulmonary embolus"
1-2	1-2	Test dose	0	Few minutes	Deep cyanosis, feeble pulse, asthmatic breathing and death after 1 to 2 cc. injected	None	
95	15	3	1:1	During injection	Sudden death without complaint during injection; sudden stopping of pulse and respirations	None	No reactions to previous injections, but lot no. 5-09 different; patient in poor condition, but sudden death unexpected

who might have had previous injections of serum were those who were immunized against diphtheria. It was impossible to determine in most instances who had received toxin-antitoxin and who had received toxoid (not containing horse serum).

DEATHS ASSOCIATED WITH ADMINISTRATION OF SERUM

During the three year period from Jan. 1, 1937 through Dec. 31, 1939, a total of approximately 5,500 cases in which the patients were treated with concentrated antipneumococcus horse serum were reported to the Bureau of Pneumonia Control. Among these there were 25 deaths (0.45 per cent) which were definitely related to administration of serum. In most instances information regarding fatal reactions was obtained personally from those observing the reaction.

The average age of the patient with a fatal serum reaction was 57.4 years. From 12 of the 25 patients (48 per cent) a history was elicited of preexisting cardiovascular disease exclusive of uncomplicated arteriosclerosis. This was twice the incidence of such disease (23.5 per cent) among all the fatalities in the 2,340 cases in which serum therapy was given from Jan. 1 to Dec. 31, 1938, exclusive of the deaths resulting from serum reactions.

Three of the 25 patients who died were pregnant women (cases 1, 4 and 25), of whom 1 (case 25) also had a history of cardiovascular disease. These pregnant patients were interesting in the light of the demonstrated burden on the circulation imposed by pregnancy and the fact that all were in the sixth or seventh month of pregnancy, when the increase in blood volume due to pregnancy reaches its peak.²⁰

A history of allergy was present in only 3 out of a total of 23 cases in which a history was reported as having been taken. One patient (case 7) had a history of eczema and hives. Another (case 9) had had asthma for three to four years previously. A third (case 25) had hay fever during childhood. The allergen in these 3 cases is unknown. Among 19 patients for whom the information was available, there was only 1 (case 12) who had received horse serum previously, the period between injections being seventeen years. A cutaneous test for sensitivity to horse serum was performed in 22 cases, and all reactions were negative. The ophthalmic reaction also was reported as negative in all of the 18 cases in which a test was performed.

20. Thomson, K. J.; Hirsheimer, A.; Gibson, J. G., Jr., and Evans, W. A., Jr.: Studies on Circulation in Pregnancy: Blood Volume Changes in Normal Pregnant Women, *Am. J. Obst. & Gynec.* **36**:48-59 (July) 1938. Cohen, M. E., and Thomson, K. J.: Studies on Circulation in Pregnancy: Summary of Studies of Physiology of Circulation of Normal Pregnant Women; New Concept of Nature of Circulatory Burden of Pregnancy and Its Application to Management of Clinical Problems of Pregnancy, *J. A. M. A.* **112**:1556 (April 22) 1939.

Only 1 (case 24) or possibly 2 (case 7 also) of the fatalities were suggestive of deaths from anaphylactic reaction due to protein hypersensitiveness. In the first instance the patient died after a small dose of serum and had asthmatic breathing as a part of the reaction. Unfortunately, the allergic history and the results of the cutaneous and ophthalmic tests were not available in this case. In the other instance the presence of asthmatic breathing and the past history of eczema and hives were possible indications of protein hypersensitiveness, although the patient had received 80 cc. of serum intravenously without reaction prior to the fatal dose. The possibility that the asthma occurring during this reaction might have been based on cardiac disease must be considered.

During the period in which these deaths from serum reactions occurred, approximately one hundred and five lots of serum were distributed. Nine of the 25 fatalities followed the injection of serum of only three of these lots, each lot being associated with 3 deaths (lots 7-06, 2B and 8-04). The fatal reactions following the use of lot 2B (in cases 16, 17 and 18) were all of the same character, consisting of a chill followed by circulatory collapse, similar to the reaction in the case reported by Cole.²¹

The fatal dose varied in amount from 1 or 2 cc. (case 24) to 99 cc. (cases 22 and 23). Death occurred immediately in some cases, while in case 19 the patient remained in collapse for two and one-half days before death. However, most patients died within one to two hours of the time that the serum was injected.

In 1 instance (case 24) death occurred during the injection of a test dose. In 13 instances death occurred during or after the first therapeutic injection, but in 10 of these the patients previously had received an intravenous test dose without reaction. In the remaining 11 cases the patients died as the result of a therapeutic injection other than the first. Therefore, 21 out of 25 patients had received some serum intravenously without reaction prior to the fatal dose.

The symptoms of the fatal reactions were fairly uniform. Practically all of these patients had vascular collapse. Only 2 (cases 7 and 24) had asthmatic breathing, and only 1 (case 16) had hives. Chills occurred in 5 patients (cases 11, 15, 16, 17 and 18), but in none were they followed by extreme hyperthermia, and all were accompanied by vascular collapse. There was no true death from hyperthermia in this series comparable to those reported in the literature.²²

21. Cole, R. I.: Serum Treatment in Type I Lobar Pneumonia, *J. A. M. A.* **93**:741-747 (Sept. 7) 1929.

22. Conner, L. A.: Experiences in New York Hospital with Treatment of Lobar Pneumonia by Serum-Free Solution of Pneumococcus Antibodies, *Am. J. M. Sc.* **164**:832-842 (Dec.) 1922. Cecil, R. L., and Larsen, N. P.: Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, *J. A. M. A.* **79**:343-349 (July 29) 1922. Heffron.⁴

TABLE 13.—Data Concerning Patients Whose Deaths During 1937,

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
1937	1	I	55 M	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
	2	I	34 F	Patient moribund	None	None	Negative	Negative	Poor	34-A	1 cc. (N. R.)†
	3	II	67 M	Unknown	None	None	Negative	Negative	Unknown	8	None
	4	II	52 M	Unknown	None	None	Negative	Not done	Moribund	Unknown	3 cc. (N. R.)†
	5	VII	71 F	Unknown	None	None	Negative	Not done	Moribund	2	None
1938	6	I	73 F	Chest tumor of bone density visible in roentgenogram; present at least 3 to 4 yr.; cause of dysphagia and dyspnea	None	None	Negative	Negative	Poor	40-A	None
	7	I	65 M	None	None	None	Negative	Negative	Moribund	40-A	None
	8	I	77 F	None	None	None	Negative	Negative	Poor	1-43A	None
	9	I	72 F	"Myocarditis and nephritis"	None	None	Negative	Negative	Poor	1-46B	None
	10	I	55 F	"Myocarditis," paranoid schizophrenia	None	None	Negative	Negative	Moribund	1-46A	None
	11	II	52 M	None	None	None	Negative	Not done	Moribund	2-18A	None
	12	II	63 M	Hypertension; enlargement of heart	None	None	Negative	Negative	Moribund	2-21D	None

* Ratio of serum to physiologic solution of sodium chloride. † N. R. indicates no reaction.

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
80	40	2	Unknown	Unknown	Death from "cardiac collapse" 1½ hours after final injection of serum started	None	No reaction to either injection indicated; no further data obtainable
120	39	3	1:1	2 min.	"Evidence of respiratory failure followed by cardiac failure"	None	Seven day interval between second and third doses; repeated cutaneous and ophthalmic reactions negative at time of fatal injection; patient moribund; relationship of serum to death difficult to decide
155	15	3	1:5	Unknown	Circulatory collapse from last 2 doses; clinical diagnosis, coronary occlusion	Bronchopneumonia in right lung; healed myocardial infarction; acute aortic endocarditis with infarcts in lungs, spleen and kidneys	
43	40	1	Unknown	30 min.	Death shortly after administration of serum; coma, cyanosis and imperceptible pulse present before serum given	None	Physician unable to decide whether serum a factor in death
10	10	1	Unknown	About 1 hr. 30 min.	Chill during injection, followed by dilatation of pupils, stiffness of joints, "skipping heart"	None	Relation of reaction to death difficult to decide
40	26	2	Unknown	3 days	Deep cyanosis, frothing at mouth at end of second injection; "almost died"	None	Condition not as good after serum reaction; survival for 3 days; physician unable to decide relation of serum reaction to death
60	20	2	0	11 min.	Administration of serum a "desperate measure" for moribund patient; after injection pulse more rapid and weak, cyanosis deeper, respirations shallower; no asthma or urticaria	None	Physician's belief, patient "dying," perhaps serum shortened life by few hours
70	20	4	1:75	40 min.	Sudden onset of pulmonary edema with rales at bases of both lungs; fall in blood pressure; increase in pulse; death	None	Physician's impression, too rapid increase in blood volume was cause of death; death not related to serum itself (1,500 cc. injected in approximately 1 hr. in a woman 77 years old)
20	20	1	0	5 min.	"No serum reaction"; "patient was dying; her heart became weaker after serum injection and she died 5 min. later"	None	Impossible to decide whether serum caused death of patient with terminal disease
20	20	1	0	Few minutes	Rolling of eyes few minutes after injection of serum; pulse more thready; respirations unchanged; no asthma or urticaria	None	Patient practically dead at time serum was administered; impossible to determine whether death would have occurred a few hours or minutes sooner if serum had been omitted
110	30	2	0	10 min.	Irregular shallow breathing; cessation of pulse and then of breathing during second injection	None	Deep cyanosis, stertorous breathing, coma and weak pulse several hours before injection
144	48	3	1:3	End of injection	Weak and irregular pulse, deep cyanosis and "early circulatory collapse before injection," increased severity of symptoms during injection; death at end of injection	None	Impossible to decide whether serum made death occur sooner than expected

TABLE 13.—Data Concerning Patients Whose Deaths During 1937, 1938

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
	13	V	70 M	Arteriosclerotic heart disease; angina pectoris	None	None	Negative	Negative	Moribund	0-05B	None
	14	V	44 M	None	None	None	Negative	Negative	Poor	5-05A	None
	15	VIII	40 F	Unknown	Unknown	Unknown	Negative	Negative	Moribund	8-03A	None
	16	VIII	44 M	None	None	None	Negative	Negative	Moribund	Unknown	None
	17	VIII	7 F	None	None	None	Negative	Not done	Moribund	8-04	1 cc.
1939	18	I	60 F	None	None	Antipneumococcus horse serum, Feb. 1938	Negative	Negative	Poor	1-58A	1 cc. (N. R.)†
	19	I	80 M	None	None	None	Negative	Negative	Poor	1-59A	None
	20	I	16 M	Rheumatic heart disease	None	Unknown	Negative	Negative	Fair	1-57A	None
	21	IV	45 M	Chronic alcoholism	Unknown	Unknown	Negative	Negative	Poor	4-04	None
	22	IV	38 M	None	None	None	Negative	Not done	Poor	4-04	None

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
60	10	2	1:14	During injection	Patient moribund; sudden death during injection when about $\frac{1}{4}$ of projected dose given	None	Physician's impression, death not related to serum in spite of occurrence during administration, since patient in terminal stage
40	40	1	1:12	Unknown	Impossible to state; data inconsistent	None	No data available beyond moribund condition of patient and death during injection
40	40	1	1:4	1 hr. 30 min.	Severe chill followed by cyanosis, shallow breathing, rapid and thready pulse and delirium	None	Although reaction severe, patient moribund; attending physician unwilling to state reaction caused death, willing to concede it might have shortened life by an hour or two
40	40	1	0	10 hr.	Slight chill, weakness, restlessness, temperature rise from 100 to 106 after reaction, pulse more rapid and weak; pulmonary edema	None	Patient thought to be moribund; physician's belief, life may have been shortened by a few hours
1	1	Test dose	1:8	20 min.	Patient moribund with almost imperceptible pulse at time of injection; patient slightly worse after injection of serum	Resolving pneumonia; purulent pericarditis	Physician's impression, patient dying; perhaps death hastened by administration of serum
120	60	3	1: $\frac{1}{2}$	10 min.	Patient moribund at time of administration of last dose; difficult to decide whether slight change in pulse after administration of serum was due to serum	None	No reactions to previous injections; normal eeg. at time of admission to hospital; in second eeg. taken after second dose changes were consistent with acute coronary thrombosis, although patient had no symptoms; patient progressively worse up to time of final injection
40	20	2	1:5	3 $\frac{1}{4}$ hr. 15 min.	"Circulatory collapse" after second dose, but patient very ill and physician doubtful that change due to serum	None	Exact relationship between administration of serum and death difficult to establish because of age and condition of patient; no reaction to first injection
40	20	2	1:25	13 hr.	Two hours after serum, chill, dyspnea and cyanosis followed by massive hemoptysis; profuse perspiration followed by rapid pulse; patient gradually worse till time of death	None	Physician doubtful whether reaction fatal in patient without severe rheumatic heart disease; intravenous injection of 500 cc. of fluid in patient with cardiac disease also a possible factor; no reaction from first injection
35	35	1	1: $\frac{1}{4}$	2 hr. 40 min.	Momentary cessation of breathing; injection stopped; after intravenous injection of epinephrine hydrochloride consciousness regained, accompanied by severe chest pain; gradually recovered from reaction; condition worse later; death	None	Physician's belief, death due to cardiac failure and not to administration of serum
20	20	1	1:1	1 hr. 15 min.	Some muscular twitching of arms and neck with rolling of both eyes and rigidity of neck; administration of serum stopped; clearing of acute symptoms; patient very ill; death 1 hr. and 15 min. after serum injected	None	Serum a possible factor in death, according to administering physician

Among those cases in which an autopsy was performed, the observations were variable. No one change was characteristic of all, except the presence of the pneumonia. The ballooning of the lungs due to acute emphysema, reported in about one half of the autopsy protocols collected by Sheppe,²³ was not observed in any of the autopsies in this series. In most of Sheppe's cases, however, there was definite evidence of protein hypersensitivity prior to the fatal reactions. Moon²⁴ expressed the belief that the pathologic changes in acute anaphylactic shock were uniform, although his definition of human anaphylaxis was vague.

In table 13, 22 cases are tabulated in which death occurred during or shortly after the administration of serum. However, other complicating factors existed, making it impossible to decide whether serum was implicated in the death of the patients. Most of the patients were moribund at the time of the administration of serum and died during or shortly after the injection. The deaths were felt by the attending physicians not to be the result of serum therapy, although a few of these cases are but slightly different from those included in table 12.

COMMENT

Thermal Reactions.—The results of this study in relation to thermal reactions coincide with those in the literature in that this type of reaction appears to depend on the lot of serum used.²⁵ However, the host factor cannot be entirely dismissed, since even the worst chill-producing lots do not cause chills in every case. Another consideration regarding thermal reactions is the route of injection of the serum. Intravenous administration is much more likely to cause such reactions than is intramuscular or subcutaneous administration.²⁶

Although there is definite evidence that the process of concentration of serum has reduced thermal reactions,¹⁸ additional factors must be considered. It is well known that laboratories producing serum may concentrate pooled serums from the same horses by the same method in two separate lots, one lot of which may be reaction free, while the other may produce severe chills. Moreover, the unconcentrated serum itself may be reaction free, while the concentrated product of the same

23. Sheppe, W. M.: Fatal Anaphylaxis in Man, *J. Lab. & Clin. Med.* **16**:372-379 (Jan.) 1931.

24. Moon, V. H.: Pathology and Mechanism of Anaphylaxis, *Ann. Int. Med.* **12**:205-216 (Aug.) 1938.

25. Leys, D.: Observations on Serum Treatment of Type I Lobar Pneumonia, *Lancet* **2**:748-751 (Sept. 30) 1933. Cecil, R. L., and Sutcliff, W. D.: Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, *J. A. M. A.* **91**:2035-2042 (Dec. 29) 1928.

26. Cecil, R. L., and Baldwin, H. S.: Treatment of Lobar Pneumonia with Subcutaneous Injections of Pneumococcus Antibody Solution, *J. Pharmacol. & Exper. Therap.* **24**:1-12 (Aug.) 1924. Kereszturi, C., and Hauptman, D.: Serum Treatment of Pneumonia in Children, *J. Pediat.* **4**:331-341 (March) 1934.

serum may produce chills.^{18a} This difference may be due to the concentration of a hypothetic chill-producing substance or to the introduction of such a substance during the process of concentration. The relationship of these chill-producing substances to the pyrogenic substances in solution of sodium chloride²⁷ also needs clarification.

Anaphylactic Reactions.—The data presented in this paper suggest that the host factor in relation to age, incidence of a history of allergy and positive cutaneous reactions is of primary importance in the occurrence of this type of reaction, in contradistinction to the importance of the serum factor among the patients who had thermal reactions.

The most probable reason for the rarity of severe anaphylactic reactions in this series lies in the selection of patients for treatment. It is evident that there must have been patients with pneumonia from whom serum therapy was withheld because of a history of hypersensitivity to horse hair, dander or serum, a strongly positive cutaneous or ophthalmic reaction or a history of recent administration of serum. Indeed, physicians often have reported verbally that a patient did not get serum for one of these reasons. If serum is withheld from such patients, no report of that fact is made to the Department of Health, and therefore the size of this group of untreated patients cannot be determined. Of all of the 2,340 cases reported in 1938, there was not one in which a history of specific allergy to horse hair or horse dander would indicate susceptibility to anaphylactic reactions to horse serum.²⁸ In considering the data in this paper, this weeding out of the sensitive patients must be kept in mind.

Circulatory Reactions.—This type of reaction seems about equally dependent on the host and on the serum factor. The host factor is important in relation to the age of the patient and the history of pre-existing cardiovascular disease, while the relation to the serum factor is demonstrated in table 12, in which groups of deaths from this type of reaction are related to certain lots of serum.

The literature contains reports of cases and deaths which appear to have been associated with this type of reaction, although the reaction was usually reported as anaphylactic. Billings²⁹ stated that in the care-

27. Hort, E. C., and Penfold, W. J.: The Dangers of Saline Injections, Brit. M. J. **2**:1589 (Dec. 16) 1911. Co Tui and Schrift, M. H.: Production of Pyrogen in Sera by Bacteria, Proc. Soc. Exper. Biol. & Med. **42**:549 (Nov.) 1939.

28. Ratner, B., and Gruehl, H. L.: Anaphylactic Crossed Relationship Between Horse Dander and Horse Serum, Arch. Path. **8**:635-644 (Oct.) 1929. Ratner, B.: Possible Explanation for Horse Serum Anaphylaxis in Man, J. A. M. A. **94**:2046-2050 (June 28) 1930.

29. Billings, F., in discussion on Park, W. H.: Is Serum Anaphylaxis a Danger of Sufficient Importance to Limit Our Use of Protective Sera in the Treatment or Prevention of Disease? Tr. A. Am. Physicians **28**:95-102, 1913.

ful administration of polyvalent antistreptococcus serum to 25 patients, "three patients nearly died of collapse" after 10 cc. of refined serum had been injected. In a report of the Therapeutic Trials Committee of the Medical Research Council,³⁰ the statement was made that the administration of a few "batches" of serum resulted in "general collapse with feeble pulse," which reaction was considered "toxic rather than anaphylactic," but no data regarding these reactions were published. Waldbott,^{5a} in an addendum to a report of 9 deaths from anaphylactic shock, described a typical fatal circulatory reaction which had been reported verbally to him and expressed the belief that it was different from the reactions reported in his paper and that it was due to "embolism." Moon²⁴ published a case report of a death due to "anaphylaxis" in a patient who showed no evidence of any type of sensitivity prior to the fatal injection; he assumed the death was related to "sensitized endothelium" of the capillaries. In that case the symptoms of a circulatory reaction were present. Bullock^{17a} published a report of 8 cases in which death was due to serum reactions, in at least 5 of which the description was that of a circulatory reaction. Heffron⁴ also reported 2 deaths from reactions which fit into this category.

The general impression resulting from a review of the literature is that all injections of protein materials resulting in death or in severe reactions other than thermal reactions are automatically called "anaphylactic" whether or not there is any evidence of hypersensitivity. A recent case report³¹ in which the patient did not present a shred of evidence of hypersensitivity is typical of that point of view. If the injected material is nonprotein in nature, the term "anaphylaxis" is not so likely to be used. Hanzlik and Karsner³² have shown that severe reactions can occur in animals from the injection of nonprotein as well as protein materials without any relation to hypersensitivity and have termed these reactions "anaphylactoid." It would seem more logical to approach the problem from the point of view that there are many varieties of reactions that can occur after the intravenous injection of foreign substances and that the anaphylactic type of reaction is but one of these.

The evidence in this paper does not indicate that anaphylactic reactions cannot occur. It does indicate, however, that fatal anaphylactic reactions are rare if proper precautions are observed. This opinion is

30. Report of the Therapeutic Trials Committee of the Medical Research Council: The Serum Treatment of Lobar Pneumonia, *Lancet* **1**:290 (Feb. 10) 1934.

31. Ziskind, J., and Schattenberg, H. J.: Fatal Anaphylactic Shock in Man, *Arch. Int. Med.* **62**:813-820 (Nov.) 1938.

32. Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from Intravenous Administration of Various Colloids, Arsenicals and Other Agents, *J. Pharmacol. & Exper. Therap.* **14**:379 (Jan.) 1920.

in agreement with that of Park.³³ On the other hand, the fact that anaphylactic reactions can be kept at a minimum in a series such as this does not mean that other types of fatal serum reactions will not occur. The deaths following serum reactions reported in this paper indicate that fatal reactions do occur in the absence of known or detectable sensitivity. Moreover, evidence is presented that particular caution must be used in the administration of serum to elderly patients or to patients with cardiovascular disease. This evidence is not in agreement, therefore, with the recent report of the Committee on Sensitization and Reactions of the American Drug Manufacturers Association,³⁴ which, in a comment on Bullova's reported cases of fatal reactions^{17a} that did not appear to be related to protein hypersensitivity, stated "There are factors which make it questionable if the serum was in any way responsible for the deaths."

If the cases of death reported in this paper are compared with those compiled by Lamson,^{3a} striking differences are apparent. The clinical picture of reaction in most of his cases is similar to that classified as anaphylactic in this paper, but quite different from that of the fatal reactions herein reported. Most of his patients were young persons who had been treated for diphtheria with serum injected intramuscularly, and most of them had a striking history of allergy and severe reactions to small amounts of injected serum. In the present series the patients were much older and received treatment for pneumonia with large amounts of serum injected intravenously. The severe reactions occurred in persons without a demonstrable sensitivity and were mostly circulatory in nature.

The evidence presented in this paper demonstrates fairly conclusively that circulatory reactions are not related to recognizable protein hypersensitivity, although the exact mechanism of this type of reaction is unknown.

Neither are circulatory reactions associated with the rapid intravenous introduction of fluids ("speed shock"),³⁵ since the rate of injection of the serum was carefully checked in those patients suffering from this type of reaction and did not exceed 1 to 2 cc. per minute in practically all cases. Moreover, the use of the "slow continuous intravenous drip method"³⁶ in a considerable proportion of the patients treated did not prevent the occurrence of these reactions.

33. Park, W. H.: Antitoxin in Diphtheria, *J. A. M. A.* **76**:109 (Jan. 8) 1921.

34. Report of Committee on Sensitization and Reactions, American Drug Manufacturers Association, *Am. Drug Manufacturers Proc.*, 1939, p. 243.

35. Hirshfeld, S.; Hyman, T. H., and Wanger, J. J.: Influence of Velocity on the Response to Intravenous Injections, *Arch. Int. Med.* **47**:259 (Feb.) 1931.

36. Hyman, T. H., and Hirshfeld, S.: Technic of Intravenous Drip, *J. A. M. A.* **96**:1221-1223 (April 11) 1931.

The most pertinent leads in the study of the mechanism of such reactions lie in certain observations on the specific effect of serum and other injected substances on the cardiovascular system. If protein decomposition products are present in certain lots of concentrated antiserum, the theory postulated by Cannon³⁷ for traumatic shock may be operative. This possibility is being explored. The injection of horse serum in dogs not previously sensitized to it changes the permeability of the pulmonary capillaries,³⁸ and the injection of defibrinated blood from a foreign species results in a sharp decrease in the coronary blood flow of the isolated heart-lung preparation of the dog.³⁹ In patients with pneumonia it has been demonstrated⁴⁰ that significant changes in the electrocardiogram occur during therapeutic intravenous injections, including those of anti-pneumococcus horse serum, even when no reactions occur. Further studies are being conducted in the hope of interpreting such changes in relation to the class of immediate serum reactions known as circulatory.

CONCLUSIONS

An analysis of data concerning a large series of patients treated with concentrated type-specific antipneumococcus horse serum by intravenous injections demonstrates that their immediate serum reactions can be grouped into three definite classes, thermal, anaphylactic and circulatory, and a fourth miscellaneous class.

That the distinction between circulatory and anaphylactic reactions is not artificial is indicated by the striking differences in the symptoms of the reactions, the age distributions and the incidence of positive histories of allergy, positive cutaneous reactions and preexisting cardiovascular disease.

A series of fatal serum reactions is reported and analyzed. Most of the fatalities followed the occurrence of a circulatory reaction.

Serious anaphylactic reactions following intravenous serum therapy are shown to be infrequent in the experience of physicians in the state of New York.

The various factors affecting the incidence of the different types of immediate reactions are discussed in the light of published data on serum reactions in man.

37. Cannon, W. B.: *Traumatic Shock*, New York, D. Appleton and Company, 1923.

38. Sherwood, N. P., and Stoland, O. O.: *Anaphylaxis: Pulmonary Permeability in Normal and Sensitized Dogs and Its Relation to Anaphylactic Shock*, *J. Immunol.* **20**:101-115 (Feb.) 1931.

39. Katz, L. N.; Weinstein, W., and Jochim, K.: *Coronary Vasoconstrictor Action of Foreign Species Blood*, *Am. Heart J.* **15**:452 (April) 1938.

40. Rutstein, D. D.; Thomson, K. J.; Tolmach, D. M., and Floody, R. J.: *Electrocardiographic Changes During Intravenous Therapy of Pneumonia*, *J. Clin. Invest.* **19**:780-781 (Sept.) 1940.

TORULA INFECTION OF THE LUNGS AND CENTRAL NERVOUS SYSTEM

REPORT OF SIX CASES WITH THREE AUTOPSIES

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LOS ANGELES

Torula infection is recognized as a rare disease caused by a yeast-like parasitic fungus belonging to the fungi imperfecti which seems to have a special predilection for the central nervous system and lungs. *Cryptococcus hominis* has recently come into rather general use as the name for the pathogenic organism of this disease.

According to Freeman,¹ Zenker's report in 1861 of a case in which involvement of the central nervous system occurred probably represents the first description of torula infection in man. As early as 1901 Vuillemin² first used the term *C. hominis* for the yeastlike organism found in the lesions of European blastomycosis. Frothingham,³ studying a tumor-like mass in the lung of a horse in 1902, discovered and described the yeastlike fungus causing the lesion. After cultural examinations and animal inoculations, he concluded the pulmonary lesion in the horse was caused by a torula. There seems little doubt the fungus he isolated was the organism now known as *Torula histolytica*.

In Germany von Hansemann⁴ and Türk,⁵ in 1905 and 1907, respectively, each reported a case of so-called blastomycosis involving the central nervous system in human beings. In this country Rusk and

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1. Freeman, W.: Torula Infection of the Central Nervous System, *J. f. Psychol. u. Neurol.* **43**:236 (Nov.) 1931.

2. Vuillemin, P.: *Rev. gén. de sc. pures et appliq.* **12**:732, 1901.

3. Frothingham, L.: A Tumor-Like Lesion in the Lung of a Horse Caused by Blastomyces (*Torula*), *J. M. Research* **9**:31, 1902.

4. Von Hansemann, D.: Ueber eine bisher nicht beobachtete Gehirnkrankung durch Hefen, *Verhandl. d. deutsch. path. Gesellsch.* **9**:21, 1905.

5. Türk, W.: Ein Fall von Hefeinfektion (*Saccharomykose*) der Meningen, *Arch. f. klin. Med.* **90**:335, 1907.

Farnell⁶ reported 2 cases of "systemic oidiomycosis" in 1911 and 1912 which have been considered due to *Torula*.

As a result of their comprehensive monograph in 1916, Stoddard and Cutler,⁷ differentiated torulosis properly from other, similar mycotic infections involving the central nervous system and applied the term *T. histolytica* to the organism. In so doing, they isolated the fungus by cultural methods, studied it further by animal inoculations and histologic sections and accurately described the clinical characteristics of the disease. They added, moreover, 2 cases to the others previously described. Since that time several comprehensive articles have been published, among them those of Freeman and Weidman⁸ in 1923, Sheppe⁹ in 1924, Stone and Sturdivant¹⁰ in 1929, Freeman¹¹ in 1931, Levin¹² in 1937 and Longmire and Goodwin¹³ in 1939.

Unfortunately, not only has the term "blastomycosis" been used for different mycoses caused by unrelated species of fungi, but undoubtedly different terms have been applied to infections produced by the same fungus. This confusion has been aggravated by the somewhat uncertain state of the terminology of these fungi. Because of the important work of Benham¹³ in 1934, however, doubt concerning the identical nature of the fungus described earlier by Busse and Vuillemin and *T. histolytica* was removed. Benham¹⁴ studied and compared the reactions and characteristics of *C. hominis* (Busse and Vuillemin) with those of *T. histolytica* and found them identical in every respect. Inasmuch as the generic term *Cryptococcus* (Kützing) em Vuillemin is commonly applied by medical mycologists to fungi imperfecti which appear only as round or oval cells reproducing by budding, she concluded that the

6. Rusk, G. Y., and Farnell, F. J.: Systemic Oidiomycosis, Univ. California Publ. Path. **2**:47, 1912.

7. Stoddard, J. L., and Cutler, E. C.: *Torula* Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

8. Freeman, W., and Weidman, F. D.: Cystic Blastomycosis of the Cerebral Gray Matter Caused by *Torula Histolytica* Stoddard and Cutler, Arch. Neurol. & Psychiat. **9**:589 (May) 1923.

9. Sheppe, W. M.: *Torula* Infection in Man, Am. J. M. Sc. **167**:91 (Jan.) 1924.

10. Stone, W. J., and Sturdivant, B. F.: Meningo-Encephalitis Due to *Torula Histolytica*, Arch. Int. Med. **44**:560 (Oct.) 1929.

11. Levin, E. A.: *Torula* Infection of the Central Nervous System, Arch. Int. Med. **59**:667 (April) 1937.

12. Longmire, W. P., Jr., and Goodwin, T. C.: Generalized *Torula* Infection: Case Report and Review with Observations on Pathogenesis, Bull. Johns Hopkins Hosp. **64**:22 (Jan.) 1939.

13. Benham, R. W.: The Fungi of Blastomycosis and Coccidioidal Granuloma, Arch. Dermat. & Syph. **30**:385 (Sept.) 1934.

14. Benham, R. W.: *Cryptococci*, J. Infect. Dis. **57**:255 (Nov.-Dec.) 1935; footnote 13.

disease resulting from these rudimentary fungi should be classified under the cryptococcoses and, in view of priority, the name given by Vuillemin, *C. hominis*, should be retained for this organism.

Not uncommonly it will be found that the protean nature of the clinical manifestations of cryptococcosis has in many instances caused the disease to be confused with tuberculous meningitis, epidemic encephalitis, syphilis and tumor or abscess of the brain. Frequently, moreover, the cause has been revealed only at the time of necropsy. That the diagnosis of torulosis may continue to be difficult and confusing is indicated by the following reports of cases of this unusual condition.

REPORT OF CASES

CASE 1.—*History*.—L. L. M., a 25 year old Filipino cook, entered the Los Angeles County Hospital Aug. 26, 1931 complaining of headache, stiffness of the neck, backache and vomiting during the previous ten days. It was also learned that about two or three weeks prior to admission he was at times confused and irrational. During the preceding three months he had complained of a sore throat. His family and past histories were found to be without significance.

Examination.—The patient seemed drowsy and appeared ill. The temperature was 99.8 F., the pulse rate 60 and the respiratory rate 22. The tonsils were not enlarged, but there was some injection of the pharynx. Pyorrhea alveolaris was noticeable. The neck was stiff on forward movement. No cervical adenopathy was noted, and nothing unusual was discovered in the heart, lungs or abdomen. The Kernig and Brudzinski signs were positive on the right and left side. The Babinski and allied signs were also positive bilaterally. No other neurologic findings were recorded at this time.

Roentgenograms of the paranasal sinuses and chest disclosed nothing unusual. A blood count made at the time of admission showed 16,700 leukocytes, with 68 per cent polymorphonuclear leukocytes. A lumbar puncture revealed a slightly cloudy fluid which was under a pressure of 28 mm. of mercury and contained 315 cells per cubic millimeter, among which the polymorphonuclear leukocytes predominated. Culture of the fluid showed no growth and no acid-fast organisms. The fluid from a lumbar puncture the following day was cloudy and contained 1,860 cells, 86 per cent of which were polymorphonuclear leukocytes and the remainder small lymphocytes. The Pandy reaction was positive. Again, the culture showed no growth, and there was no evidence of acid-fast organisms.

The Wassermann reactions of both the blood and the spinal fluid were negative.

Stiffness of the neck, diplopia in all directions and recent choking of the optic disks, with overfilling of the vessels, were noted in the examination on September 2. The deep reflexes of the lower extremities were more hyperactive on the right side than on the left, and although the Babinski and allied signs were positive bilaterally, they were more strongly positive on the right side than on the left. Tuberculous meningitis was thought the most likely diagnosis at this time.

Daily lumbar punctures were performed. The cell count varied from 400 to 3,000 per cubic millimeter of spinal fluid. The pressure of the spinal fluid increased gradually, being reported over 400 mm. of fluid after September 13. On September 12 the content of sugar in the spinal fluid was 19 mg., of chlorides 673 mg. and of total protein 660 mg. per hundred cubic centimeters. Cultures

continued to be sterile, and no acid-fast bacilli were found. It was not until September 15 that torulas were discovered in the spinal fluid. This identification was confirmed by the department of mycology.

Course.—The patient continued to be irrational and drowsy. After September 2 right hemiparesis gradually developed, and the choking of the optic disks became more apparent. Bilateral paresis of the sixth nerve also became evident at this time. His temperature varied between 100 and 101 F., except on two occasions, when it was 104 F. Unfortunately, at his death, on Sept. 21, 1931, permission for autopsy was refused.

CASE 2.—History.—E. P., a 36 year old white man, a laborer, was in good health until March 6, 1933, when he experienced severe frontal headaches. Some three days later he vomited several times and thereafter was distressed by nausea and vomiting. He continued working but fainted on two occasions a few days prior to hospitalization at the Los Angeles County General Hospital. With the onset of his illness he was at times confused and complained also of dimness of vision. The day prior to admission his neck was stiff and his back painful. He had also felt feverish at times and drowsy. The family and past history as obtained revealed nothing of consequence.

Examination.—The patient was roused with some difficulty. The temperature was 100.2 F., the pulse rate 60, the respiratory rate 18 and the blood pressure 124 systolic and 76 diastolic. Nothing noteworthy was discovered in the general physical examination. Examination of the cranial nerves revealed equal but slightly irregular pupils which reacted sluggishly to light. Although his visual acuity was markedly diminished, this could not be tested accurately because of his illness. The fundi showed blurring of the margins of the disks, with overfilling of the veins. Partial left homonymous hemianopia was also described. Nothing abnormal was reported in the remaining cranial nerves. Except for a bilaterally positive Kernig sign, the general neurologic examination revealed nothing remarkable.

Roentgenograms of the chest and skull made March 24 disclosed nothing unusual. On admission the leukocyte count was 11,800, with 80 per cent polymorphonuclear leukocytes. Lumbar puncture revealed a pressure of 250 mm. of spinal fluid, which was slightly cloudy. The cell count was 770, and 84 per cent of this number were polymorphonuclear leukocytes. The Pandy reaction was negative. The impression at this time was that of tuberculous meningitis.

A lumbar puncture the following day showed pus cells and budding yeastlike bodies on the smear. No growth was obtained on culture. A subsequent lumbar puncture revealed a pressure of 375 mm. of spinal fluid, which was slightly cloudy and contained 590 cells. The Gram stain showed many small, gram-positive, round objects, some of which appeared to be budding. A study of the fluid by the department of mycology led to the identification of *T. histolytica*. The patient's condition became rapidly worse, and he died March 25.

Autopsy.—The calvarium appeared normal. The pia-arachnoid showed diffuse and moderate opacity, the thickening being most marked along the superficial vessels and sulci. In some places small, discrete tubercles were present along the blood vessels. The convolutions of the brain were moderately flattened, slightly more on the right side than the left. The pial surfaces were congested, and in many places there were small hemorrhages. Many small hemorrhages were found on the left frontal operculum. At the base of the brain were small collections of exudate in the sulci and the basilar cisterns. The middle ears, mastoid cells and accessory nasal sinuses revealed no inflammatory changes.

The lungs were hyperemic and moderately edematous. No bronchopneumonia or granulomatous lesions were found. Except for slight arteriosclerotic involvement of the coronary arteries, the heart appeared normal. The liver weighed 1,720 Gm., and the various cut surfaces revealed cloudy swelling. The spleen was slightly softened and enlarged, weighing 240 Gm. The other organs examined disclosed nothing grossly abnormal.

Microscopic Examination.—In the brain a marked increase in the number of interstitial cells was noted in the subcortical white matter. These cells were also more numerous in the deeper layers of the cortex. The subarachnoid space was loaded with inflammatory exudate, which consisted of round cells and fewer polymorphonuclear leukocytes. Yeast cells were found in large numbers free in the exudate and within large phagocytic cells. No lesions due to *Torula* were found in the other organs examined histologically.

CASE 3.—*History.*—M. S., a 25 year old white man, was well until about two months prior to admission to the Los Angeles County Hospital on April 9, 1933, when he complained of nausea and vomiting. About two weeks prior to hospitalization, the onset of fever and constant, severe frontal headache occurred and he noticed blurred vision. He gave no history of unconsciousness, convulsions or incontinence. The family and past histories were noncontributory.

Examination.—The patient responded slowly to questioning and complained of severe headache. The neck was slightly stiff in forward movement. Otherwise nothing unusual was discovered in the general physical examination.

The neurologic examination as recorded revealed external deviation of the left eye. The pupils were round, regular and equal. They responded poorly to light. Examination of the remaining cranial nerves and the general neurologic examination disclosed nothing noteworthy.

Roentgenograms of the paranasal sinuses, chest and skull revealed nothing unusual. The erythrocyte count was 4,100,000 and the leukocyte count 7,150, with 84 per cent neutrophils. An initial pressure of over 400 mm. of spinal fluid was obtained on lumbar puncture. The cell count was 227 per cubic millimeter, with 14 per cent polymorphonuclear leukocytes and 86 per cent lymphocytes. No organisms were seen on the smear, and no growth was obtained on culture. The Wassermann reactions of both the blood and the spinal fluid were negative.

Daily lumbar punctures were performed. The pressure was invariably high and the cell count between 100 and 300 per cubic millimeter. The smears continued to show no organisms and the culture no growth. It was not until April 15 that fluid obtained by cisternal puncture revealed a few cells and yeastlike bodies on the smear. Cultures yielded the same organisms, which were identified as *T. histolytica* by the department of mycology.

Course.—The patient failed to improve and remained restless and irrational. The temperature varied between 99 and 101 F. He was taken home, against advice, April 30 and died a few weeks later. Permission for an autopsy was not obtained.

CASE 4.—*History.*—A. C. L., a girl aged 15 years, was seen in consultation with Dr. Robert L. Cunningham at the Hospital of the Good Samaritan, Los Angeles, June 16, 1938. Her present illness began in India in August 1937 with headache, nausea and vomiting. At times her vision became blurred, and on some occasions she saw double. She also noticed some stiffness of the neck. During this time she had a slight fever and some morning cough, raising sputum.

After the onset of her illness, she was taken to the Carmichael Hospital for Tropical Diseases at Calcutta, India, at which time a palpable spleen was noted.

Nothing unusual was discovered in the neurologic examination. She had a leukocyte count of 10,200 per cubic millimeter, with 68 per cent polymorphonuclears. Results of tests for undulant fever were reported as negative. Lumbar puncture revealed fluid under moderate pressure. It was clear but showed a few cells with the lymphocytes predominating. Azosulfamide (the disodium salt of 4-sulfamidophenyl-2'-azo-7'-acetylaminio-1'-hydroxynaphthalene-3', 6'-disulfonic acid) was given parenterally with no noticeable improvement.

Two months after the onset of her symptoms a roentgenogram of the chest revealed interlobar empyema on the right side, and for this reason she was operated on October 30. An examination of the pus showed no organisms, and the culture was reported as sterile. The material removed at operation consisted mainly of fibrous tissue, with signs of chronic inflammation.

A second lumbar puncture on Dec. 2 showed a pressure of 290 mm. of spinal fluid. The smear revealed a fairly large number of polymorphonuclear cells but no organisms, and the culture was sterile. At this time the Wassermann reaction of the spinal fluid was reported as positive and the Wassermann reaction of the blood as doubtfully positive. Roentgenograms of the skull revealed a beaten-silver appearance with the convolutional markings greatly increased. On Jan. 1, 1938 dimness of vision was first noticed, more pronounced in the right eye. On ophthalmologic examination the optic disks were pale, particularly that of the right eye.

On February 7, with the use of avertin with amylene hydrate and local anesthesia, a right frontal craniotomy was performed. The dura was opened and the brain found to be under increased pressure, but no evidence of an abscess was discovered. Subsequent to this procedure, she was free of vomiting and headache for about three weeks, after which the symptoms gradually recurred. Her post-operative convalescence was otherwise essentially uneventful. Ophthalmoscopic examination March 8 showed considerable progression of the optic atrophy in each eye. Because this seemed primary and the Wassermann reactions were positive, syphilis was believed to be the cause. The family and past histories, however, were not significant.

The patient returned with her mother to California, their previous home, April 23. Although her general condition improved during the trip, she had a slight rise in temperature in the afternoon and fatigued easily; the chest sinus continued draining.

Examination.—Examination at the Hospital of the Good Samaritan revealed an apathetic, pale and rather emaciated white girl of 15 years, weighing about 80 pounds (36.3 Kg.). Her temperature was 98.6 F., her pulse rate 108 and her respiratory rate 22. A well healed right frontal craniotomy scar was evident; associated with this was a small decompression, which was not under pressure. The head was freely movable in all directions, without stiffness of the neck. Inspection of the chest revealed a drainage site in the region of the second right interspace anteriorly in which an iodoform wick was present. With the exception of dulness over the right upper part of the chest, the percussion note was resonant throughout, and no rales were heard. There was no precordial enlargement; the heart sounds were clear and regular, and no murmurs were heard. The abdomen and extremities were not remarkable.

Examination of the cranial nerves revealed definite pallor of both optic disks, more pronounced on the right than on the left. The appearance was that of primary optic atrophy. The pupils were found to be circular and equal, though somewhat dilated. They reacted sluggishly to light but well in accommodation. The extra-ocular movements were normally performed. Examination of the other cranial nerves disclosed nothing abnormal. The visual fields appeared slightly constricted to rough testing. The patient was not well enough for a perimetric examination.

In view of her general weakness, the motor power of the extremities was not significantly lessened. Sensation was intact throughout, and tests for coordination gave normal results. The deep and superficial reflexes were equal and active; the Babinski and allied signs, negative. The blood pressure was 120 systolic and 80 diastolic.

Roentgenograms of the chest on June 16 revealed an area of density extending outward and slightly upward from the right hilus. This density lay entirely in the anterior part of the chest, and part of it appeared to involve the interlobar fissure. There was no evidence of a cavity or fluid level within this density, and the rest of the pulmonary field was clear (fig. 1). Roentgenographic study of the skull showed the presence of the right frontal craniotomy wound, which was well healed, without evidence of infection of the bone. The sella was a little

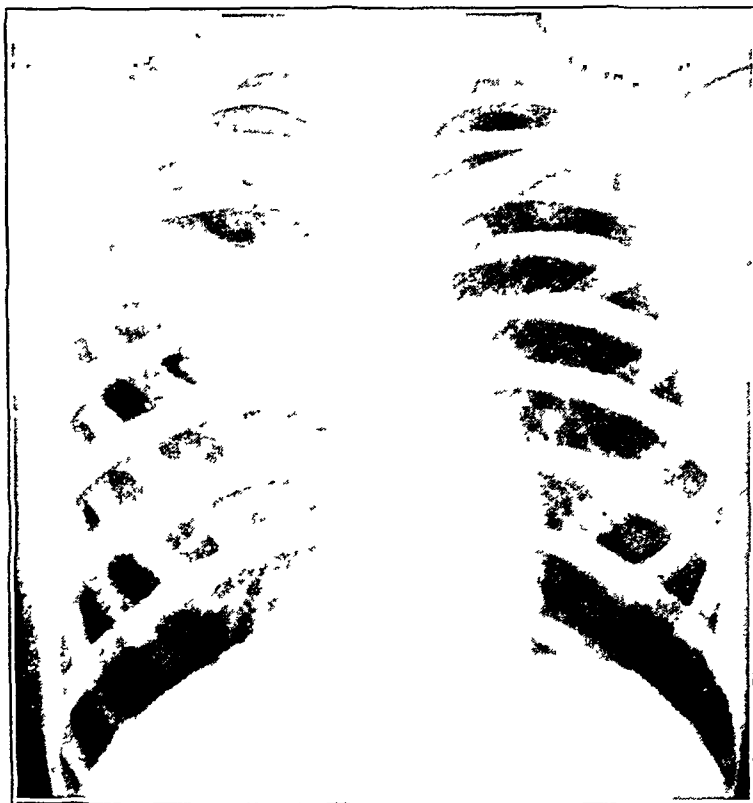


Fig. 1 (case 4).—Roentgenogram of the chest taken June 16, 1938.

larger than normal but revealed no evidence of erosion. The convolutional markings were considerably accentuated.

Urinalysis disclosed nothing abnormal. Examination of the blood revealed a hemoglobin content of 67 per cent, an erythrocyte count of 4,010,000, a leukocyte count of 7,100, with 65 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, 7 per cent monocytes and 1.5 per cent eosinophils, and a negative Wassermann reaction of the blood. A lumbar puncture June 17 registered a pressure of 200 mm. of spinal fluid, which was slightly cloudy, contained 73 cells per cubic millimeter, with polymorphonuclears predominating, and showed 175 mg. of protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative, but the colloidal gold curve was 5555554211.

Some of the purulent fluid was aspirated from the draining sinus in the chest. Microscopic examination of a wet mount preparation showed numerous polymorpho-

nuclear leukocytes and numerous round, double-contoured bodies, surrounded by a clear zone, resembling *T. histolytica* (fig. 2). Gram stain of a smear revealed numerous polymorphonuclear leukocytes and a moderate number of gram-positive, yeastlike bodies. *T. histolytica* was grown in culture.

A second examination of the spinal fluid on June 23, with the removal of about 8 cc. of slightly cloudy fluid, revealed 92 cells per cubic millimeter, 16 per cent polymorphonuclear leukocytes and 84 per cent lymphocytes. Cultures made from the centrifuged material produced a growth of *T. histolytica*. Injection of this material into mice produced the characteristic lesions of *Torula* (fig. 3), and typical colonies were again grown from the material taken from these lesions.

The patient was discharged from the hospital June 25, and returned to her home in Pomona, Calif. She was given 15 grains (0.97 Gm.) of potassium iodide daily.

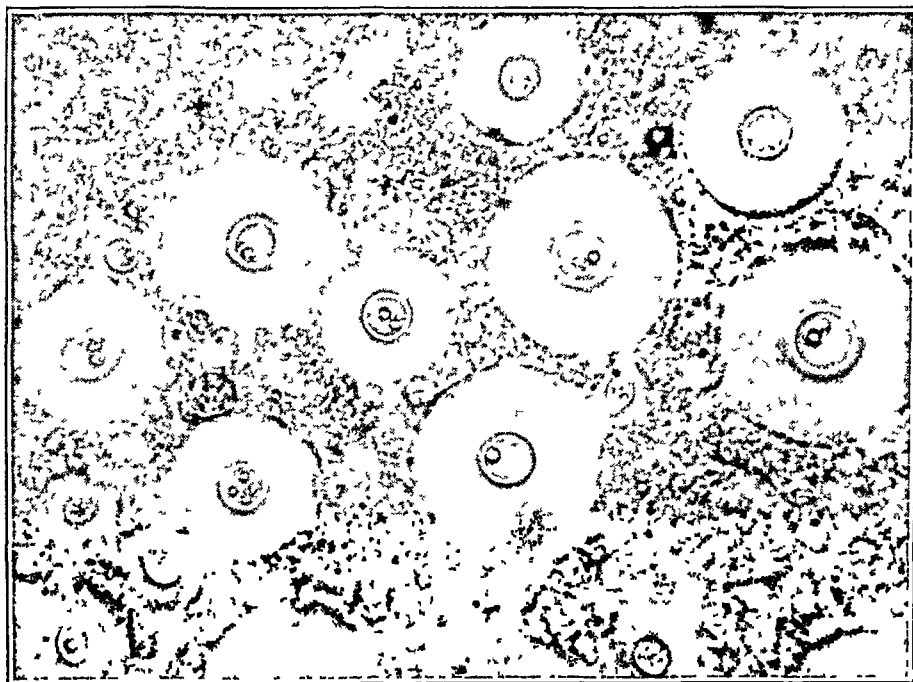


Fig. 2 (case 4).—Photomicrograph of an unstained wet mount preparation of material from the discharging chest sinus. The mucinoid envelop is seen as a clear zone or halo surrounding each organism. $\times 500$.

Second Admission.—She was admitted March 29, 1939 to the Hospital of the Good Samaritan through the Good Hope Clinic for reexamination and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) therapy. Whereas previously she weighed 80 pounds (36.3 Kg.), her weight was now 97 pounds (44 Kg.) (fig. 4). Until January 1939 she suffered occasionally with headaches, after which they no longer occurred. She realized her vision had improved and that she felt stronger. Although her chest continued draining, she was no longer troubled with coughing. She also commented on the fact she felt much more alert mentally. During September 1938 her periods, which had ceased during her illness, returned and remained regular.

At this time it was found she could not read with her right eye, but could count fingers at a distance of 1 foot (30 cm.). With her left eye she was able

to read the headlines of a newspaper. The results of neurologic examination were otherwise essentially unchanged. Stereoroentgenograms of the chest and a right lateral projection disclosed that the abnormal density springing from the right hilus, noted previously, had shrunk in all diameters.

A cell count of 87, showing 34 per cent polymorphonuclears, 65 per cent lymphocytes and 1 per cent eosinophils, was found on examination of the spinal fluid. A wet mount preparation from the centrifuged specimen revealed no yeastlike bodies.



Fig. 3 (case 4).—Photomicrograph of a section of mouse lung. The mouse died after an intraperitoneal inoculation of the cerebrospinal fluid from the patient in case 4. Hematoxylin and eosin stain; $\times 500$.

Cultures of the same, however, disclosed a few colonies of *T. histolytica*. Material taken from the chest sinus contained numerous yeast cells. *T. histolytica* grew on culture mediums.

On March 30 the patient was given 20 grains (1.29 Gm.) of sulfapyridine four times daily, which dosage was changed to 15 grains (0.97 Gm.) five times daily on March 31. A concentration of sulfapyridine of between 9 and 13 mg. per hundred

cubic centimeters of blood was maintained. This treatment was continued until her discharge from the hospital April 8.

Third Admission.—She was readmitted to the hospital May 16, with evidence of further improvement. The drainage from the chest had become less profuse. Examination gave essentially the same results as previously, except that she seemed stronger and more alert. The neurologic findings were essentially unchanged. The visual fields were charted; although she fatigued easily, with a large object the left field was outlined fully, while the right showed a large and somewhat irregular defect over most of the temporal area.

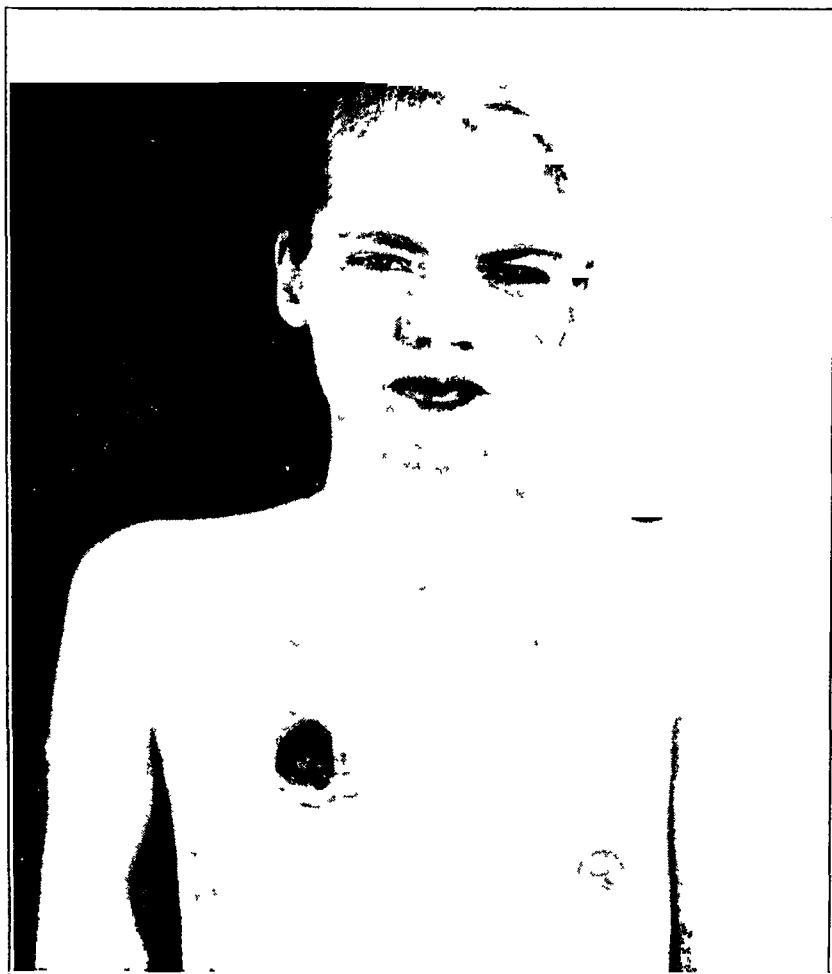


Fig. 4 (case 4).—Photograph of the patient during her second admission to the hospital, March and April 1939. The sinus in the right side of the chest is plainly visible, and the healed scar of the craniotomy in the center of the forehead is also apparent.

Roentgenograms of the chest and the results of fluoroscopic observation May 18, when compared with those last made, showed that the triangular area running upward and outward from the right hilus was much smaller. Nothing suggesting new spread or reinfection was seen.

Numerous pus cells and a moderate number of torulas were present in the exudate from the chest sinus. Lumbar puncture showed a pressure of 250 mm. of spinal fluid, with 117 cells per cubic millimeter and a total protein content of

350 mg. per hundred cubic centimeters. She was given 20 grains (1.29 Gm.) of sulfanilamide four times daily, which maintained a concentration of sulfanilamide of 9 to 12 mg. per hundred cubic centimeters of blood. She tolerated her treatment well and was discharged May 26.

Fourth Admission.—She was readmitted December 16. She had gained about 15 pounds (6.8 Kg.), so that her weight on this admission was 113 pounds (51.3 Kg.). She stated that the chest sinus was smaller and was certain she had gained in strength, mentioning that she could walk a mile (1.6 kilometers) without tiring. Her periods continued to be regular. Her vision was essentially unchanged. Examination disclosed a decrease in the size of the chest sinus with less evidence of granulation tissue. The patient appeared more alert. Charting revealed no change in the visual fields.



Fig. 5 (case 4).—Roentgenogram of the chest Dec. 18, 1939. The improvement in the condition of the chest is readily apparent.

Roentgenograms and fluoroscopic examination of the chest showed that there had been a remarkable decrease in the amount of density of the upper field of the right lung, there being only a small amount of residual fibrotic-appearing density at the level of the second rib anteriorly near the hilus (fig. 5). A lumbar puncture disclosed a pressure of 200 mm. of spinal fluid, which was clear and colorless, with a cell count of 46 per cubic millimeter. The total protein was 225 mg. per hundred cubic centimeters. No organisms were observed in a wet-mount preparation of the centrifuged sediment, but a few colonies of torulas were obtained on Sabouraud's medium.

On December 16 she was given 0.1 cc. by intradermal injection and 0.1 cc. by subcutaneous injection of undenatured torula antigen 1 (Krueger). On December 19, 0.1 cc. was given by intradermal injection and 0.2 cc. by subcutaneous injection.

On December 23, an injection of 0.1 cc. was given intradermally and of 0.3. cc. subcutaneously. She tolerated the treatment well and was discharged December 23, to continue taking potassium iodide. She has remained about the same since that time. Fluid obtained by lumbar puncture April 17, 1940 contained 66 cells per cubic millimeter, had a total protein content of 140 mg. per hundred cubic centimeters, showed no organisms on microscopic examination and yielded only 2 colonies of *T. histolytica* on 2 dextrose agar slants and a dextrose agar plate.

CASE 5.—History.—B. M. M., a 52 year old laborer, entered the Santa Fé Hospital Jan. 28, 1938 complaining of dull frontal headache of six weeks' duration. This followed a cold, which had cleared up in a few days. The headaches persisted and gradually became more severe. He was able to continue working until two weeks prior to hospitalization, when there developed general malaise, night sweats, fever and some drowsiness.

Examination.—The patient was rather drowsy and appeared ill. The temperature was 99 F., the pulse rate 82, the respiratory rate 20 and the blood pressure 160 systolic and 110 diastolic. Otherwise the general physical examination revealed nothing unusual. A neurologic examination was not recorded, but it was observed that his pupils were equal and active and the Babinski reaction negative.

Examination of the blood on January 29 revealed a hemoglobin content of 105 per cent; an erythrocyte count of 5,210,000; a leukocyte count of 17,300, with 92 per cent polymorphonuclear leukocytes and 8 per cent lymphocytes; a negative Wassermann reaction of the blood, and a culture negative after forty-eight hours. A cell count of 46 per cubic millimeter, with lymphocytes predominating, was found on examination of the spinal fluid. The Pandy reaction was negative and the sugar content normal. No organisms were found. Another puncture two days later revealed 23 cells, with a normal content of globulin and sugar. On this occasion both the smear and the culture showed the presence of yeast cells. Yeast cells were also found in the smears and cultures on six subsequent examinations of the spinal fluid. The cell counts of these specimens varied from 190 to 300 mm. per cubic millimeter. The fungus found in the spinal fluid was identified as *T. histolytica*.

The patient's condition failed to improve, and he died February 22. His temperature varied between 99 and 104 F., with an average of 100 to 101 F. He was given azosulfamide parenterally, without beneficial effect, and remained irrational and stuporous most of the time.

Autopsy.—An autopsy was performed by the coroner's department and the brain examined by Dr. C. B. Courville. Except for slight widening of the sulci in some areas, the convolutions of the brain appeared normal. Close inspection of the leptomeninges disclosed a peculiar mottled appearance, which seemed due to an unusual striation of fibrinous reticulum in the subarachnoid space. This reticulum was formed of tiny nodules, some no larger than a pinpoint. This was noted particularly over the frontal lobes. A few small nodules were found around the basilar surface of the cerebellum. Sections of both cerebral hemispheres disclosed a small isolated spot in the basilar cortex on the left side. In the right hemisphere another small lesion, measuring about 2 by 1.5 cm., was found in the external capsule. The ventricles were lined with granulation tissue. Sections through the cerebellum and brain stem failed to disclose any additional lesions.

Microscopic Examination.—Many lymphocytes, a few polymorphonuclear leukocytes and numerous yeast cells were present in the pia-arachnoid spaces of the

brain. Microscopic examination of the bone marrow, lungs, kidneys, spleen and liver showed no evidence of torula infection.

CASE 6.—History.—B. C. M., a 24 year old mechanic, entered the Los Angeles County Hospital Sept. 19, 1939 complaining of vomiting and occipital headaches during the preceding week. About two months prior to hospitalization he noticed a small furuncle on his left wrist, which persisted for about two weeks. It was



Fig. 6 (case 6).—Photomicrograph of torulas in the meninges. $\times 230$.

also stated that he coughed up reddish brown sputum a few days before his entry, but none thereafter. The family and past histories were without significance.

Examination.—The patient complained of severe headache and appeared ill. His neck was stiff. Except for a slight systolic murmur at the apex, nothing unusual was discovered on examination of the chest, and the rest of the physical examination disclosed nothing remarkable. A complete neurologic examination was not recorded, but it was noted that he had slight weakness of the left side of the face,

his deep reflexes were noticeably diminished and the Babinski sign was negative bilaterally. On admission it was believed the patient had meningitis, possibly tuberculous.

A pressure well over 400 mm. of spinal fluid was found on entry. The cell count was 235 per cubic millimeter; the chlorides measured 690 mg. and the total protein 72 mg. per hundred cubic centimeters. Microscopic examination of

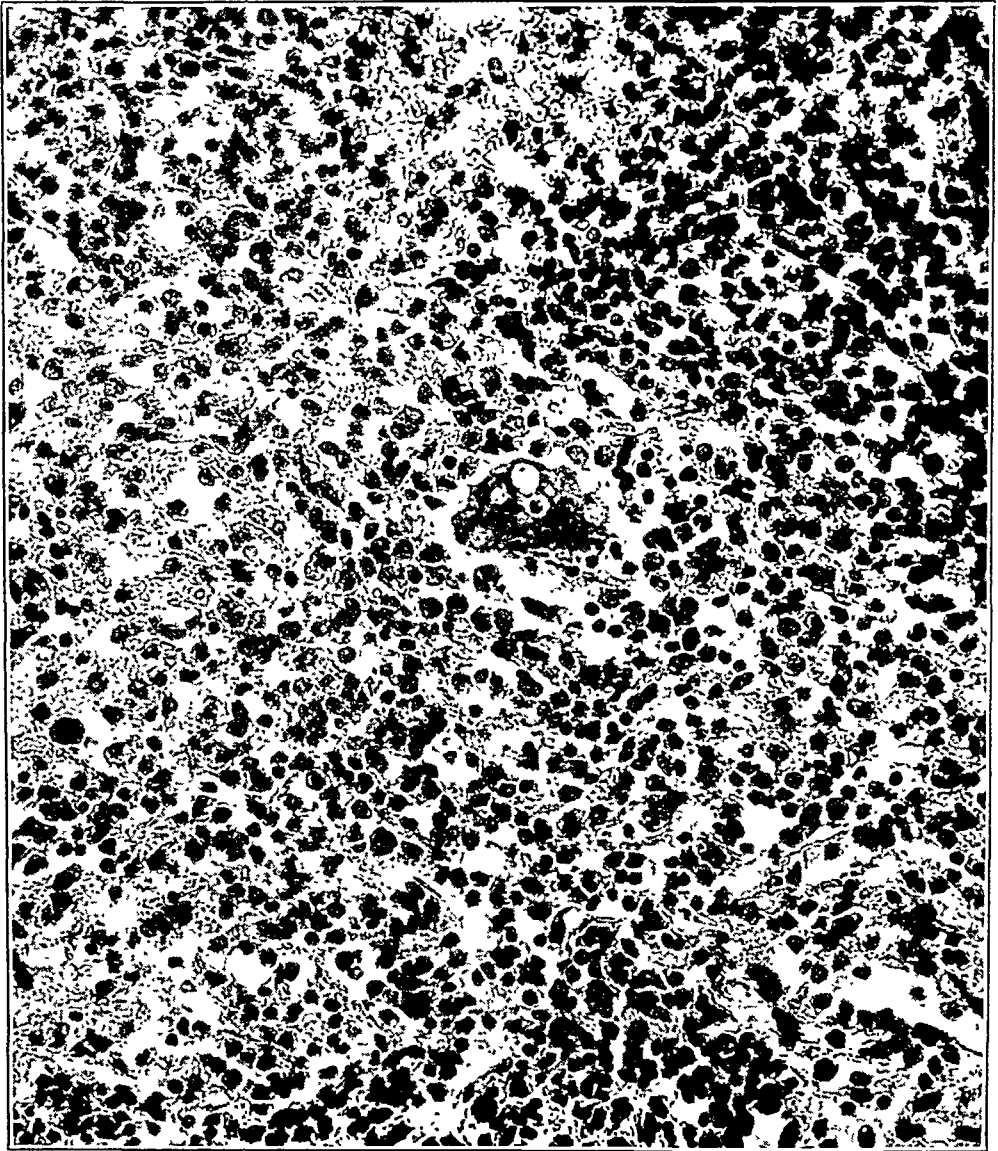


Fig. 7 (case 6).—Photomicrograph of a giant cell containing torulas in the spleen. $\times 345$.

the sediment revealed numerous yeast buds morphologically resembling *T. histolytica*. This diagnosis was confirmed by culture of the spinal fluid.

Roentgenograms of the chest disclosed nothing pathologic. The Wassermann reactions of both the blood and the spinal fluid were negative. Daily spinal punctures disclosed similar high pressures and cell counts, ranging between 100 and 500 per cubic millimeter. Torulas were found on all smears and cultures. The

patient was given sulfanilamide, the concentration of which in the blood was maintained between 10 and 20 mg. per hundred cubic centimeters. Three days prior to his death, on November 29, this was changed to sulfapyridine. His course was progressively downhill. A postmortem examination was made and the brain examined by Dr. C. B. Courville.

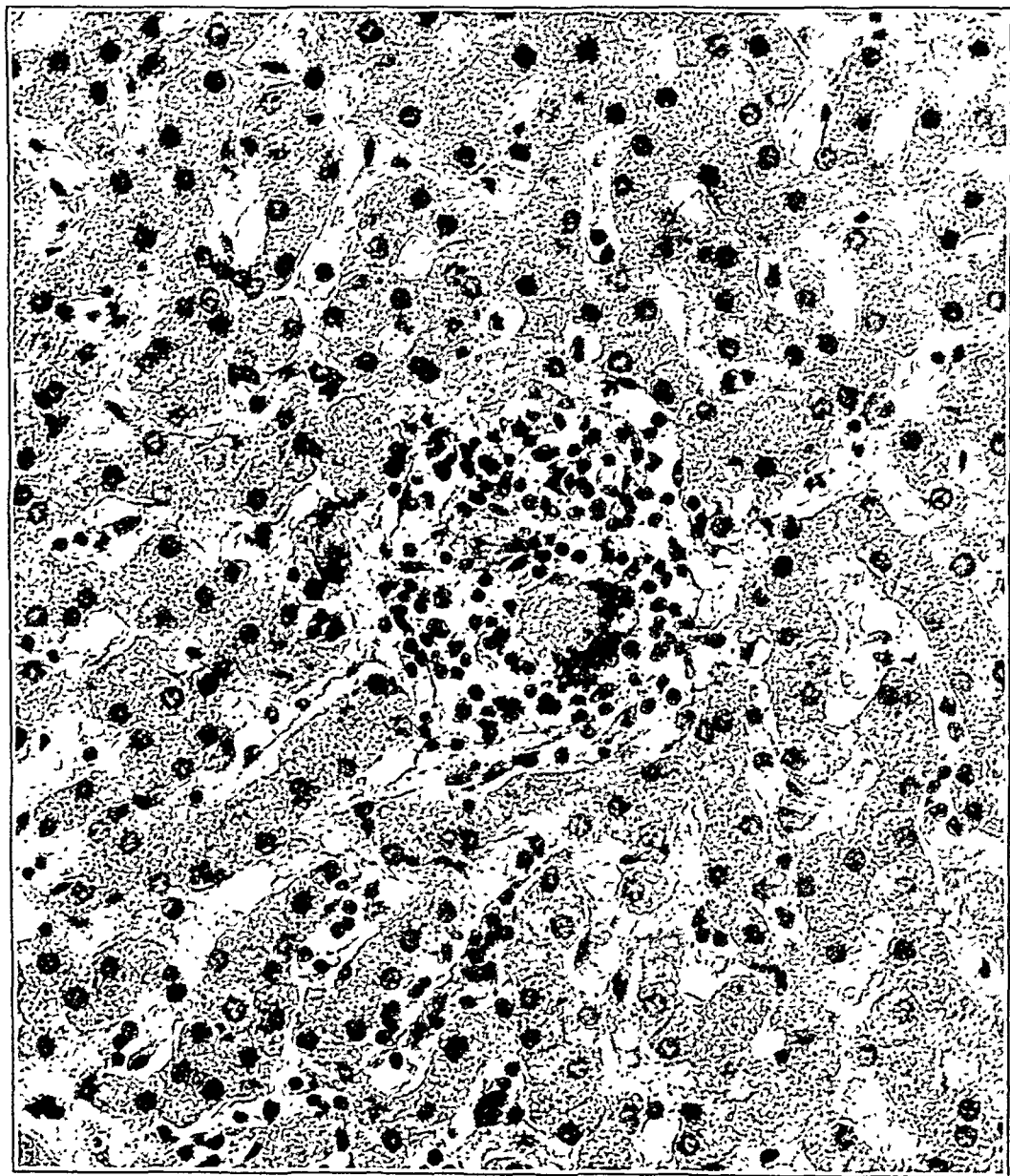


Fig. 8 (case 6).—Photomicrograph of a tubercle and giant cell containing torulas in the liver. $\times 345$.

Autopsy.—The convolutions of the brain were somewhat flattened. Small accumulations of exudate were found in the sulci. In one place tubercles were discovered at the base of the brain along the vessels. There was some herniation of the cerebellar tonsils.

The heart was normal in appearance and weighed 300 Gm. A few small hemorrhages were found in the pleura. The parenchyma of the lungs was moder-

ately congested, hemorrhagic in places and free of granulomatous lesions. The liver weighed 2,200 Gm. The markings and color were within normal limits. The weight of the spleen was 900 Gm. The follicles were enlarged. The pulp was firm and dark red. The kidneys together weighed 390 Gm. and were normal except for congestion and parenchymatous degeneration.

Microscopic Examination.—Brain: Varying amounts of granulation tissue and round cell infiltration containing small and large yeast cells were seen in the pia-arachnoid space (fig. 6). In some areas the yeast cells were present in large numbers, around which there was little tissue reaction. Budding was noticed in many of the cells. Just below the pia a few poorly defined tubercles containing many yeast cells were found. Deeper within the brain substance the granulomatous process involved some of the Virchow-Robin spaces. One section of the cervical portion of the cord presented the same histologic picture as that in the pia-arachnoid space. In this section one tubercle was found deep within the white matter.

Other Organs: There was a definite increase of reticulum of the spleen and an occasional siderosclerotic nodule. In a few isolated areas yeast cells were found in giant cells and free in the pulp (fig. 7). The pulp in places was diffusely infiltrated with varying numbers of polymorphonuclear leukocytes, round cells and eosinophils. The kidneys were interesting in that a number of glomerular tufts contained small areas of necrosis, in which yeast cells were found. In a section of an adrenal gland two small tubercles with central areas of necrosis contained yeast cells. Similar lesions in small numbers were found in the sections of the liver (fig. 8). The section of a lung revealed a few areas of hemorrhage involving the air spaces, thickened alveolar walls infiltrated with small numbers of polymorphonuclear leukocytes and round cells. In some of the thickened alveolar walls giant cells containing yeast bodies were found. We believe this case represents another example of generalized torula infection.

All of the organisms in these 6 cases were identified by culture and animal inoculation by Dr. John F. Kessel, of the department of mycology of the Los Angeles County Hospital. He also reproduced torula meningitis in monkeys with each of the cultures.

DIAGNOSIS AND CLINICAL PICTURE

As was previously intimated, not only may the antemortem diagnosis of torula infection be difficult, but frequently it is not made. The first 2 cases reported by Cutler and Stoddard were in Dr. Harvey Cushing's service at the Peter Bent Brigham Hospital. As mentioned by Cushing, in a discussion on a paper by Shapiro and Neal,¹⁵ in both there were symptoms of intracranial pressure without localizing features, operation was without avail and the diagnosis was made only at autopsy. In his 60 collected cases, Levin¹¹ found the condition diagnosed prior to death in 37 instances and at autopsy in 23 instances.

Often the onset of the disease is insidious with intermittently severe frontal headaches, but not infrequently it may be sudden with headaches more pronounced and associated with spells of vomiting. Dizziness, vertigo and stiffness and pain in the back of the neck are not uncommon

15. Shapiro, L. L., and Neal, J. B.: Torula Meningitis, Arch. Neurol. & Psychiat. 13:174 (Feb.) 1925.

symptoms, and visual disturbances, such as amblyopia, diplopia, strabismus, nystagmus and ptosis, are also reported rather frequently. Mental symptoms, including confusion, drowsiness, restlessness and delirium, have been described commonly. Ataxia and hemiplegia have also been noted.

The commonest physical symptom has been stiffness of the neck, with positive Kernig and Brudzinski signs. Fever, if present, is of only moderate degree, and the leukocyte count is usually not much elevated. Neuroretinitis and papilledema are frequently seen. The reflexes have been variably reported. Occasionally the Babinski sign is obtained. Although occasional periods of remission have been noted, the course of the disease is usually downhill, and the patient ultimately becomes comatose and dies of respiratory failure. If the lungs are involved, the clinical picture may suggest tuberculosis or tumor. There is usually a cough, some pain in the chest, malaise and loss of weight, but little or no fever or night sweats.

In the cases reviewed by Levin,¹¹ it is interesting to discover that prior to culture or autopsy, tuberculous meningitis was diagnosed in 10 instances, undesigned meningitis in 5, encephalitis in 7, tumor and abscess of the brain in 6 and 4, respectively, and psychotic dementia in 5. He reported involvement of the central nervous system alone in 30 cases and of the lungs in 9 cases and generalized involvement in 8 cases.

One to six months has been the usually recorded duration of the disease. In Levin's ¹¹ series of 60 cases, however, he found the duration of the illness to be one month or less in 3 cases, two months in 10, twenty-five to thirty months in 5 and six years in 1.

PORTAL OF ENTRY

In most instances the respiratory tract has been considered the route by which the cryptococcus enters the body. Freeman and Weidman⁸ suggested the tonsils as a portal of entry. Some have expressed the opinion that the parasite gained entrance by way of the gastrointestinal tract. In a case reported by Johns and Attaway¹⁶ the initial lesion was found to be a small superficial granuloma which developed from a razor cut and resulted in meningitis, with characteristic organisms in the cerebrospinal fluid.

INCIDENCE

In 1925 Shapiro and Neal¹⁵ collected a total of 15 cases of torula infection, including 1 of their own. In 1930 Freeman¹⁷ reviewed the

16. Johns, F. M., and Attaway, C. L.: *Torula Meningitis: Report of Cases and Summary of Literature*, *Am. J. Clin. Path.* **3**:459 (Nov.) 1933.

17. Freeman, W.: *Torula Meningo-Encephalitis: Comparative Pathology in Nineteen Cases*, *Tr. Am. Neurol. A.* **56**:203, 1930.

gross and histopathologic changes observed in 19 cases of torulosis and in his monograph in 1931¹ reported a total of 43 cases. Since that time Levin¹¹ found 15 more which, with the 2 he reported in 1938, brought the total to 60 cases of invasion of the central nervous system by *Torula*. Including the cases recently reported by Taber,¹⁸ Caldwell,¹⁹ Crone,²⁰ Quodbach,²¹ Cudmore and Lisa,²² de Busscher and his associates,²³ Greenfield, Martin and Moore,²⁴ Longmire and Goodwin,¹² Magruder,²⁵ D'Aunoy and Lafferty²⁶ and Robertson and his associates,²⁷ together with our cases reported here, the total number is now 79. In view of the early misleading reports on the identity of such fungous infections, however, one is forced to be somewhat hesitant about accepting the accuracy of the number of these cases reported in the literature to date, but their occurrence has at all events been relatively uncommon.

CLASSIFICATION AND DIFFERENTIATION OF THE BLASTOMYCETES

Similarity of the characteristics and activities of the fungi comprising the blastomycetes requires some consideration of their differentiating features. It should be stated, however, that none of the numerous classifications proposed has been generally adopted and any discussion of the classification of the yeasts and molds is open to criticism. In this group cryptococcosis, or torula infection, blastomycosis, or oidiomycosis, and coccidioidal granuloma are the ones most apt to be confused. The saccharomycetes, or true yeasts, involve the skin usually to a mild extent only; the monilia attacks the mucous membranes, mouth, gastrointestinal

18. Taber, K. W.: Torulosis in Man, *J. A. M. A.* **108**:1405 (April 24) 1937.

19. Caldwell, G. T.: Systemic Cryptococcosis with Report of Case, *Texas State J. Med.* **33**:310 (Aug.) 1937.

20. Crone, J. T.; DeGroat, A. F., and Wahlin, J. G.: Torula Infection, *Am. J. Path.* **13**:863 (Sept.) 1937.

21. Quodbach, K.: Ein Beitrag zur Pathologie der Blastomykose der Zentralnervensystems, *Zentralbl. f. allg. Path. u. path. Anat.* **69**:227 (Feb. 20) 1938.

22. Cudmore, J. H., and Lisa, J. R.: Torula Meningo-Encephalitis: A Case Report, *Ann. Int. Med.* **11**:1747 (March) 1938.

23. de Busscher, J.; Scherer, H. J., and Thomas, F.: La méningite à *Torula* (contribution à l'étude des localisations nerveuses des infections à pseudolevures), *Rev. neurol.* **70**:149 (Aug.) 1938.

24. Greenfield, J. A.; Martin, J. P., and Moore, M. T.: Meningo-Encephalitis Due to *Cryptococcus Meningitidis* (*Torula Histolytica*), *Lancet* **2**:1154 (Nov. 19) 1938.

25. Magruder, R. G.: Torula Infection of the Central Nervous System: Three Cases, *J. Lab. & Clin. Med.* **24**:495 (Feb.) 1939.

26. D'Aunoy, R., and Lafferty, C. R.: Torula Meningitis in Child, *Am. J. Clin. Path.* **9**:236 (March) 1939.

27. Robertson, W. E.; Robertson, H. F.; Riggs, H., and Schwartz, L.: Torulosis Involving the Human Cerebrum, *J. A. M. A.* **113**:482 (Aug. 5) 1939.

tract, lungs and intertriginous portions of the skin, while *C. hominis*, *Oidium dermatitidis* and *Coccidioides immitis* frequently involve the central nervous system. In the case of the mycoses due to the last two organisms, however, invasion of the nervous system is usually secondary to or associated with involvement elsewhere, particularly of the skin or subcutaneous tissues.

The similarity of *C. hominis* to *O. dermatitidis* and *C. immitis* invariably requires differentiation of these fungi by means of morphologic characteristics, cultural reactions and animal inoculation, in which case the identity can be established with certainty. Although the methods of distinguishing these fungi and the differences in their pathologic picture are interesting and important phases of mycology as related to *C. hominis*, it was not considered within the scope of this article to review this subject, which is so well discussed in such standard texts as those of Zinsser and Bayne-Jones²⁸ and Gay.²⁹

The importance of examination, culture and animal inoculation of the spinal fluid in cases of obscure cerebrospinal diseases, especially those characterized by severe headache without a definite cause, becomes readily apparent.

MORPHOLOGIC AND CULTURAL CHARACTERISTICS

The cells of the pathogenic torula measure from 1 to 13 microns in diameter. Budding, which constitutes their only method of reproduction, is invariably evident, the buds having thinner walls than the mother cell, the walls of which may be highly refractile. Surrounding the organisms in the tissues there is practically always a clear zone composed of gelatinous material, which constitutes a characteristic feature of the lesion and which caused Stoddard and Cutler to name the parasite *T. histolytica*. The organism itself is surrounded by a thick capsule of mucoid material. In artificial cultures the morphologic characteristics are practically the same except that no capsules are formed. Within the cells may be seen numerous granules, many of which are composed of a fatty material, as shown by the sudan III stain. In sections the cells stain irregularly, but a thick wall is usually visible.

The artificial growth of *Torula* consists of forms practically identical with those seen in the tissues, having no resemblance to molds and consisting of yeastlike budding organisms. Gelatin shows only slight liquefaction after six or eight weeks, and no gaseous fermentation of the sugar occurs. On the various agar mediums containing dextrose the

28. Zinsser, H., and Bayne-Jones, S.: Textbook of Bacteriology, ed. 8, New York, D. Appleton-Century Company, Inc., 1939, pp. 746-751.

29. Gay, F. P.: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935, pp. 1109-1151.

fungus produces a moist, cream-colored growth, which often becomes yellow or darkened with age. On maltose agar the colony assumes a deep brown color.

PATHOLOGY

C. hominis is pathogenic for mice and rats, while rabbits, guinea pigs and dogs have been found only slightly susceptible. Intraperitoneal injections into rats and mice result in lesions involving the meninges, brain, lungs, liver and spleen, with the peritoneum but slightly affected.

In human beings there is a predilection for the central nervous system and the lungs; visceral involvement is much less common. The skin and skeletal systems have been rarely affected, the site of the lesions differing in this respect from that in the diseases due to the two related organisms. According to Ball,³⁰ 4 instances have occurred in which the infection was localized. In the case of Brewer and Wood³¹ the infection affected the muscles of the vertebral column, in that of McGehee and Michelson,³² it was localized to a pelvic and inguinal abscess, in that of Berghausen³³ to the tongue and in that of Jones³⁴ to the nasopharynx. Kessel and Holtzworth³⁵ reported an interesting case of torula infection of the knee. Rappaport and Kaplan,³⁶ Weidman³⁷ and Mook and Moore³⁸ reported torulosis of the skin. Levin¹¹ found 8 cases of generalized torula infection, and Longmire and Goodwin¹² added another.

With the exception of the cerebrospinal system, torula infection results in a defensive cellular reaction, similar to that observed in the tissues of infectious granulomas generally. The lesions, consisting of small nodules or tubercles, varying from 0.5 to 8 mm., have as one of their most striking characteristics a large content of mucinous material, evidently a product of their parasitic growth. As the tissue is invaded

30. Ball, H. A.: Human Torula Infections: A Review, California & West. Med. **32**:338 (May) 1930.

31. Brewer, G. E., and Wood, F. C.: Blastomycosis of the Spine; Double Lesion; Two Operations; Recovery, Ann. Surg. **48**:889, 1908.

32. McGehee, J. L., and Michelson, I. D.: Torula Infection in Man, Surg., Gynec. & Obst. **52**:803 (June) 1926.

33. Berghausen, O.: Torula Infection in Man, Ann. Int. Med. **1**:235 (Oct.) 1927.

34. Jones, E. L.: Torula Infection of the Nasopharynx, South. M. J. **20**:120 (Feb.) 1927.

35. Kessel, J. F., and Holtzworth, F.: Experimental Studies with Torula from a Knee Infection in Man, Am. J. Trop. Med. **15**:467 (July) 1935.

36. Rappaport, B. Z., and Kaplan, B.: Generalized Torula Mycosis, Arch. Path. **1**:720 (May) 1926.

37. Weidman, F. D.: Cutaneous Torulosis, South. M. J. **26**:851 (Oct.) 1933.

38. Mook, H. W., and Moore, M.: Cutaneous Torulosis, Arch. Dermat. & Syph. **33**:951 (June) 1936.

by the fungus, it becomes dissolved and replaced by the parasites and their covering, with little evidence of inflammatory reaction. Particularly in tissues other than the central nervous system, the structure of the nodules may be like that of miliary tubercles, composed of giant, epithelioid and lymphoid cells with few polymorphonuclear leukocytes. The torula organisms may or may not be visible in the lesions. Each organism is seen to be surrounded by a circular zone of homogeneous, clear and slightly basic-staining mucin. The presence of caseation has been considered the result of lytic action of the organisms or their products. In the older lesions areas of hyalinization may be discovered.

The reaction of the tissues in the cerebrospinal type of disease is reportedly less marked. Freeman¹⁷ classified the 'gross pathologic process under three types, the first of which he described as the chronic meningeal form, with diffuse granulomatous meningitis resulting in meningeal thickening and cortical adhesions. Microscopically, the picture resembled a lytic process of the brain substance produced by the invading parasites without an adequate inflammatory-reparative reaction. The second, or perivascular, form, with small granulomas or cysts in the cortex, extended from the surface of the brain along the course of the vessels into the cerebral parenchyma. He found the perivascular type associated frequently with the meningeal. In the third, or embolic, form the lesions were deeply placed, lying chiefly in the gray matter of the basal ganglions, although occasionally in the white matter of both the cerebellum and the cerebrum. Stoddard and Cutler⁷ and Freeman¹⁷ have also noted degenerative changes in the ganglion cells with increased neuroglia formation and degeneration of myelin sheaths.

Longmire and Goodwin¹² criticized such a classification. After studying the types of lesions reported, they found cases in which all degrees of cellular reactions in the brain and meninges were shown. They therefore expressed the opinion that with the gradual shading of one type of reaction into the next it was difficult to make any sharp separation of the cases into three distinct classes. It was their experience that the degree of resistance offered to the growth of the fungus from tissue to tissue, even in different parts of a single organ, varied as much as did the general resistance in different persons. Crone, DeGroat and Wahlin²⁰ found a similar variability in different patients.

COMMENT

As can be appreciated from the preceding case reports, the course of torula infection in case 4 was strikingly different from that in the others, in which death occurred within a few months, the usually recorded duration of the disease. At the time of writing the duration of illness in case 4 has been more than two and half years, which, though

longer than usually recorded, is not longer than has occasionally been noted. In view of the improvement, it will be interesting to discover whether or not this case is another instance of a remission or the beginning of recovery. Inasmuch as no patients with cerebrospinal torulosis have reportedly survived, it seems that eventual recovery is unlikely. Such a noticeable variation in the duration of the illness must be related in some way to a difference in the general resistance of the host, as well as to a variation in the virulence of the fungus.

Although various methods of treatment have been attempted, none has been of any significant benefit. Although the fourth case represents one of the first opportunities for the use of sulfapyridine in treatment of this infection, improvement in this case was evident prior to its trial. Sulfapyridine was also used three days prior to the death of the patient in case 6, without any beneficial effect. Interestingly, in the fourth case both the culture of the spinal fluid and the culture obtained from the involved area of the lung during the course of illness in India failed to reveal the presence of the fungus. This may have been due to the fact that the cultures were not given sufficient time for the organism to make its appearance on ordinary mediums. The importance of further examinations under such circumstances becomes evident and is further emphasized by the fact that in the first and third cases numerous cultures and examinations were made before the organism was discovered.

With the exception of the fourth case, in which the condition was first thought due to syphilis because of the positive Wassermann reactions, the presumptive diagnosis was tuberculous meningitis. Although the proper diagnosis was established in all cases prior to death or autopsy, it was made possible only by the laboratory data.

Because of the pathologic condition, case 6 was felt to represent another example of generalized torula infection.

SUMMARY AND CONCLUSIONS

Torulosis, or cryptococcosis, is a chronic fungous infection which, because of its protean manifestations, simulates tuberculous meningitis, tumor or abscess of the brain or encephalitis when involving the central nervous system, for which it has a special predilection.

Its diagnosis, often difficult, as evidenced by the presented cases, can only be ascertained by the growth of the fungus from the spinal fluid and its differentiation by laboratory methods from other infectious granulomas, such as blastomycosis and coccidioidal granuloma.

That the condition is uncommonly experienced is shown by the fact that when the presented cases are included with those recently reported the total number collected at the present time is only 79.

In spite of various efforts at treatment, none has proved effective, and in all proved cases of involvement of the central nervous system the disease has always progressed to a fatal termination. Our fourth case is of interest because there has been continued improvement in spite of a duration of the illness of more than two and a half years. Our sixth case represents, we believe, a generalized type of the infection.

The noticeable variation in the duration of torula meningitis must be related in some way to a difference in the general resistance of the host, as well as to a variation in the virulence or type of the fungus.

FUSOSPIROCHETOSIS

RECOVERY OF THE CAUSATIVE ORGANISMS FROM THE BLOOD, WITH REPORT OF TWO CASES

ROBERT H. WILLIAMS, M.D.

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Although a large number of spirochetal diseases have been described, in only a few have the causative organisms been cultured from the blood. Larson and Barron¹ observed a patient with Vincent's stomatitis and osteomyelitis who died after seven weeks of a severe febrile illness. Two days before death a sample of the patient's blood was cultured on ascitic agar in a Novy anaerobic jar at 37 C. After a few days fusiform bacilli appeared in the culture. Attempts were made to subculture these organisms on plain agar, ascitic broth, plain broth, ascitic agar and Löffler's blood serum. No aerobic growth was observed. Growth occurred in all of the anaerobic cultures except the one containing plain agar only. Optimum growth occurred on ascitic agar. When horse blood agar was used some of the organisms exhibited a few spirals. Larson and Barron expressed the belief that the spiral organisms were modified forms of the fusiform bacilli, but they did not describe in detail the characteristics of the spiral structures. Rabbits, guinea pigs, mice and rats were inoculated. Intravenous, subcutaneous, intraperitoneal, intratesticular and intraocular injections were made, with negative results.

Reiter² observed a patient with cystitis, arthritis and conjunctivitis. Blood cultures in blood-ascitic beef broth yielded spirochetes, which possessed from seven to ten spirals and exhibited boring movements. No fusiform bacilli were observed. The spirochetes stained intensely with Löffler's methylene blue (methylthionine chloride) and were pathogenic for mice.

Videla and Rey³ studied a patient who had Vincent's angina, enlargement of the cervical lymph nodes and phlebitis of some of the veins

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1. Larson, W. P., and Barron, M.: Report of a Case in Which the Fusiform Bacillus Was Isolated from the Blood, *J. Infect. Dis.* **13**:429-437 (Nov.) 1913.

2. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), *Deutsche med. Wchnschr.* **42**:1535-1536 (Dec. 14) 1916.

3. Videla, C. A., and Rey, J. C.: Angina de Vincent. Septicemia venosa subaguda, *Rev. Asoc. méd. argent.* **47**:1898 (Jan.) 1933.

of the neck. Fusiform bacilli and spirochetes were observed in smears of the pharyngeal exudate. Cultures of the blood yielded no growth. Nevertheless, on the basis of the clinical picture, the condition was diagnosed as "subacute venous septicemia."

Palmer⁴ recently observed a patient who had a prolonged illness, with vague pains in the muscles and joints, relapsing fever, a rash resembling that of German measles, arthritis and pericarditis. No organisms were cultured from the blood, but spirochetes, measuring about 15 microns in length and possessing three to five spirals, were demonstrated many times in dark field preparations. Blood from the patient was inoculated intraperitoneally into a rat. Spirochetes in the rat's blood were discovered ten days after inoculation. The type of spirochete was not established.

In May 1938 there was admitted to the Vanderbilt University Hospital a patient with arthritis from whose blood fusiform bacilli and spirochetes were subsequently cultured eleven times. After this experience it became the custom in the clinical bacteriologic laboratory to culture all specimens of blood both aerobically and anaerobically and to examine specimens of the blood cultures under dark field illumination. In July 1938 fusiform bacilli and spirochetes were recovered from the blood of a second patient with multiple arthritis and an acute febrile illness.

Fusospirochetal infections are common, and metastatic lesions are not infrequent. The occurrence of the latter indicates that invasion of the blood stream sometimes takes place. Nevertheless, actual recovery of the organisms from the blood has been rare. In fact, the only instance of proved fusospirochetemia which we have found in a survey of the literature is that reported by Larson and Barron.¹ Consequently, a detailed account of the 2 cases observed at Vanderbilt University is presented.

REPORT OF CASES

CASE 1.—E. D., a bus driver aged 28, was admitted to the hospital May 18, 1938 complaining of arthritis. He had considered himself well until July 1936, although for several months preceding this time a creamy urethral discharge had been present. On July 28, 1936 fever developed, with severe headache and generalized malaise. Within a short time most of the joints of the extremities became swollen, red and tender, and he became delirious. After approximately seven weeks of severe illness a tonsillectomy was performed. Three days later his sensorium became normal; fever disappeared shortly thereafter. The condition of the joints exhibited considerable improvement, but soreness and stiffness were noticed periodically. The left leg had been immobilized in a cast for five

4. Palmer, L.: Spirochetal Blood Stream Infection of Undetermined Type: Report of Case, *South. M. J.* **31**:530-534 (May) 1938.

weeks during the acute illness. After removal of the cast, the ankle and knee remained stiff.

In January 1938 gonococci were obtained from the urethral discharge. The patient was treated by means of urethral irrigations and by the use of sulfanilamide. However, urethritis persisted, and he was admitted to the hospital for fever therapy.

Physical Examination.—The temperature was 99 F., the pulse rate 88, the respiratory rate 18 and the blood pressure 148 systolic and 94 diastolic. The patient did not appear ill. His nutritional state and muscular development seemed good. No abnormalities of the skin or the mucous membranes were observed. The epitrochlear lymph nodes were slightly enlarged, but the superficial nodes elsewhere were of normal size. The tonsils and teeth had been removed. Examination of the heart and lungs revealed no abnormalities. The liver could not be felt, but the edge of the spleen was palpable 6 cm. below the left costal margin. The splenic surface was firm and smooth but not tender. The left knee was swollen and appreciably limited in motion. The left ankle and the phalangeal joints of the left foot were almost completely ankylosed. A slight increase in the temperature of the skin over the left ankle was noted, but there was no edema.

Laboratory Data.—The urine was normal. The leukocyte count was 4,900 per cubic millimeter, the hemoglobin content 15 Gm. per hundred cubic centimeters and the Wassermann reaction of the blood negative. Many gram-negative intracellular diplococci were found in the urethral discharge. The complement fixation test for gonococcic infection was positive. Roentgenograms revealed narrowing of the joint apexes of the left knee and left ankle and marked roughening of the articular surfaces. The patient's serum in a dilution of 1:1,280 agglutinated *Bacillus abortus* and *Bacillus melitensis*. The opsonocytophagic test for brucellosis revealed marked phagocytosis by most of the cells. The patient exhibited a strong intradermal reaction to 0.1 cc. of brucellergen.

Course.—The first hyperthermal treatment was given May 20, without noticeable change in the patient's condition. On May 23 a second hyperthermal treatment was administered, his temperature being maintained between 106 and 107 F. for five hours. Two days after this treatment he experienced nausea, epigastric distress, a shaking chill and elevation of temperature to 104 F. (fig. 1). On May 27 he was slightly jaundiced (icterus index 21). There appeared in the skin of the legs and trunk many hot, round, erythematous lesions, 5 to 20 mm. in diameter. They were not raised or tender. Some of the lesions had a purplish tinge (fig. 2). Two blood cultures were made on this day. (See "Bacteriologic Studies.") One week later both cultures were found to contain fusiform bacilli and spirochetes.

On May 28 the patient complained of pain low in the left axilla, and the following day a pleural friction rub was heard over this area. It disappeared after forty-eight hours. The jaundice subsided in a few days and did not recur.

A third hyperthermal treatment was given June 6, and a fourth was begun two days later but was discontinued because of the development of marked shortness of breath and abdominal cramps.

On June 14 intravenous injections of 0.6 Gm. of neoarsphenamine were instituted at intervals of about seven days. Febrile reactions followed several of these treatments. On July 4 the reaction to neoarsphenamine was so severe that it was

decided to employ silver arsphenamine in the future. The patient received weekly injections of 0.3 Gm. of silver arsphenamine and biweekly injections of 2 cc. of a 1.5 per cent solution of bismuth sodium tartrate for the next three months. After the first injection of bismuth a sharp and more prolonged febrile reaction developed, but none occurred subsequently.

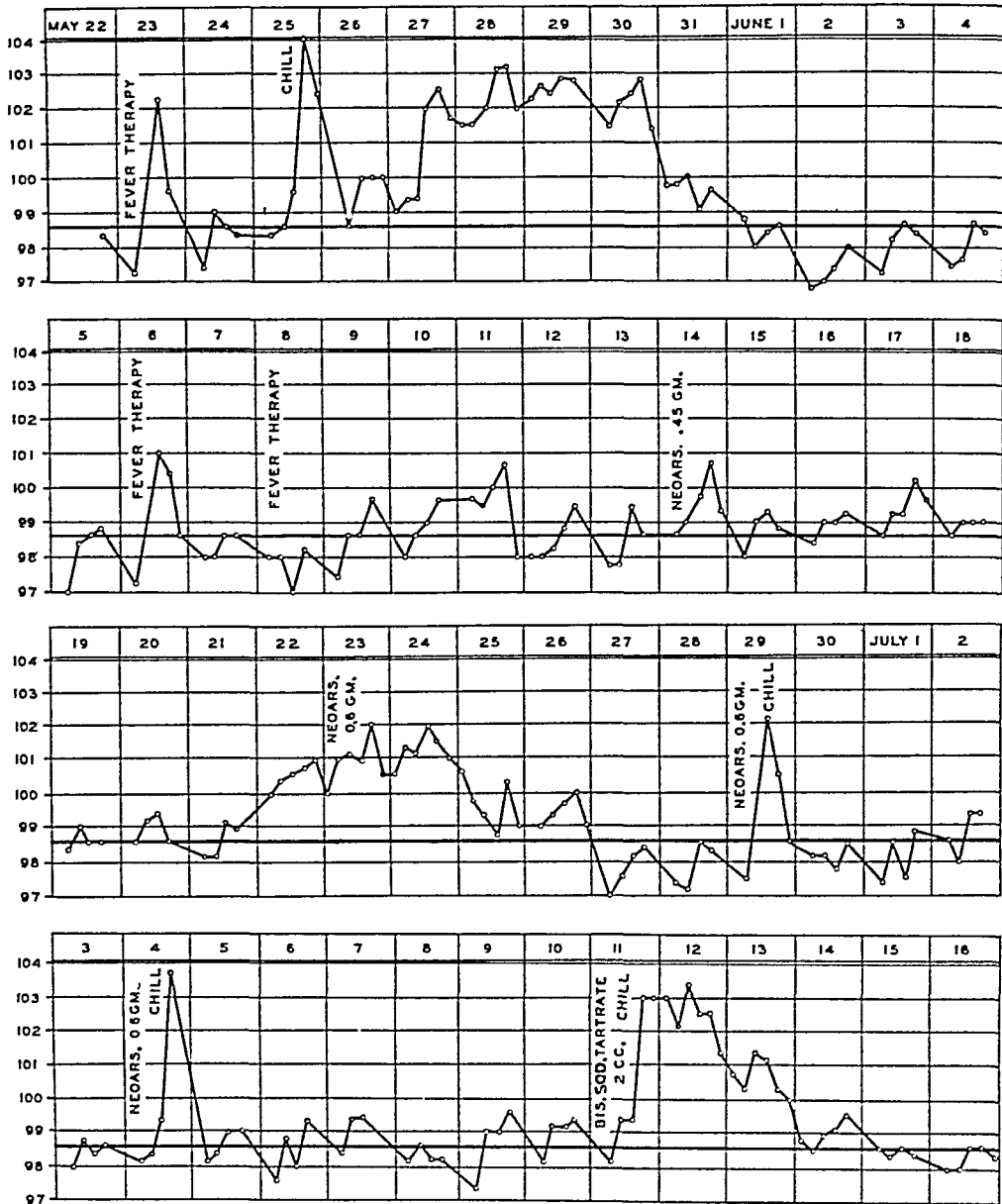


Fig. 1 (case 1).—The temperature chart. Note reactions to treatment.

The patient remained in the hospital two months. He complained of slight pain in the joints from time to time. They occasionally exhibited evidence of mild, acute inflammation. The splenic enlargement persisted, and the erythematous lesions were still present at the time of the patient's discharge from the hospital.

Throughout his stay in the hospital cultures of the blood were made periodically. Spirochetes and fusiform bacilli were demonstrated in eight of a total of thirteen

such cultures. Several dark field examinations of the patient's blood were made, but no organisms were revealed. Furthermore, neither fusiform bacilli nor spirochetes were found in the urine, stools or urethral discharge by either dark field examination or culture.

A year and a half has elapsed since the first admission of the patient to the hospital. His course has been followed closely in the outpatient department, and he has been readmitted to the hospital twice for study. During this elapsed period he has been out of bed most of the time and in general has felt well.



Fig. 2 (case 1).—Erythematous eruption with hemorrhages in some areas.

The cutaneous rash disappeared in September 1938 and did not recur. He has had two bouts of fever. In January 1939 his temperature rose daily to about 102 F. for a few days and in June to about 104 F. In both attacks he experienced persistent aching pain in the joints. During the year and a half the results of physical examination have not changed. The abnormalities of the joints have remained stationary, and splenic enlargement has persisted.

After the patient was discharged, blood cultures were made monthly for ten months. Three of these yielded fusospirochetes. The last positive culture was

obtained Oct. 11, 1938, three months after the termination of his first stay in the hospital. Seven subsequent cultures were negative. The characteristics of the organisms are recorded below.

Special Bacteriologic Studies.—On May 27, 20 cc. of the patient's blood was drawn into 20 cc. of a 1.5 per cent solution of sodium citrate. Cultures were made as follows: Portions measuring 0.5, 1.0 and 1.5 cc. were mixed with 3 per cent beef infusion agar (p_H 7.6) and poured into Petri dishes. A tube of beef infusion broth containing sterile ascitic fluid was also inoculated. The remaining blood was placed in a 300 cc. Florence flask containing dextrose-infusion broth (p_H 7.7) to which had been added 20 cc. of sterile ascitic fluid. One of the blood agar plates and the two broth cultures were covered with a layer of sterile melted petrolatum.

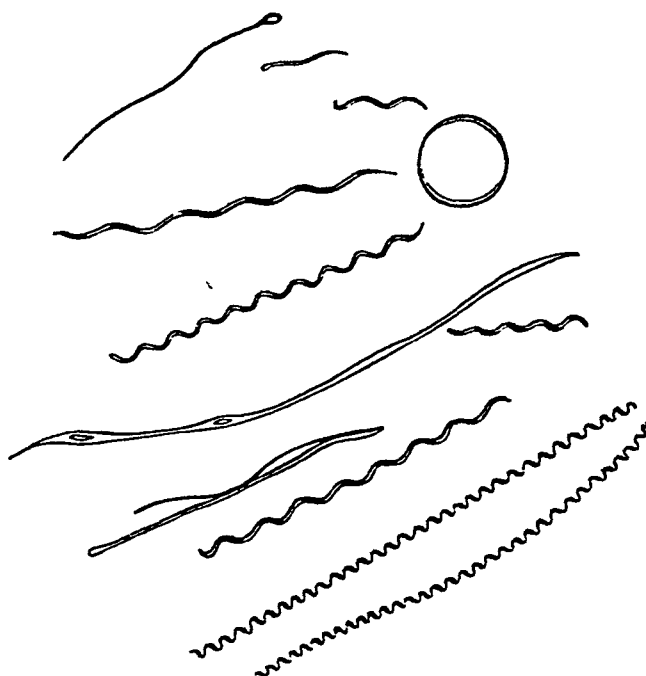


Fig. 3 (case 1).—Drawing ($\times 2,250$) of various organisms observed in a dark field preparation of a blood culture. Note the extreme pleomorphism.

All of the cultures were incubated at 37 C. After two days the broth in the flask appeared cloudy, and slight hemolysis was present. On microscopic examination actively motile, slightly gram-positive, fusiform rods were observed. No organisms were found in the other cultures. The flask was placed in a jar of carbon dioxide under 75 mm. pressure. At the end of three days increased turbidity and hemolysis was observed. Smears stained by the Gram method revealed no organisms, but the examination of wet preparations by bright and by dark field illumination revealed the presence of many spirochetes. These organisms were subcultured nine times. The culture was then discarded.

As has been stated, twenty-three cultures of the blood were made, and eleven yielded fusiform bacilli and spirochetes. Many of the strains of these organisms were subcultured repeatedly.

Morphologic Characteristics: One of the most outstanding characteristics of the organisms was their pleomorphic nature (figs. 3, 4 and 5). Measurements of

several hundred spirochetes gave the following results: length, 6 to 45 microns, with an average of 15 microns; width, 0.4 to 0.8 micron, with an average of 0.6 micron; spiral amplitude, 2 to 6 microns, with an average of 3 microns, and spiral depth, 1.2 to 2.5 microns, with an average of 1.8 microns. The number of spirals varied from two to thirty-five, with an average of five. In some organisms the spirals were close together, but in the majority they were widely spaced. Some of the spirals were irregular. The ends of the organisms were sharply pointed. Some of the larger organisms had a double contour. No flagella, crista or chambered structure was observed. The fusiform bacilli varied somewhat in size but the average length was about 10 microns and the average width 0.8 micron. The ends were tapered and pointed.

The commonest type of motion was of a corkscrew-like, boring variety, although serpentine motion was observed. At times the larger spirochetes moved like earthworms and rarely exhibited rotary movements. There was great variation in the speed of motion, the smaller forms moving more rapidly. The fusiform bacilli darted back and forth quickly in a shuttle-like fashion.

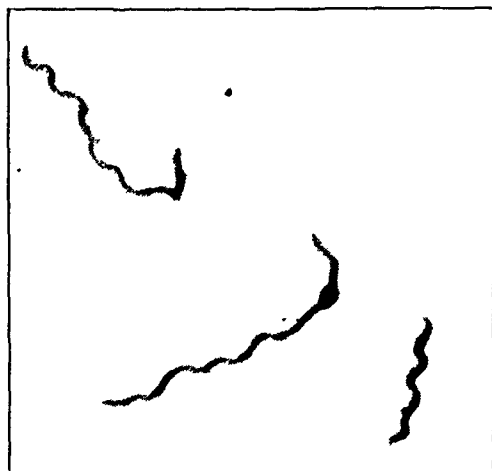


Fig. 4 (case 1).—Spirochetes ($\times 2,000$), stained by Fontana's method, in a blood culture.

Multiplication was by transverse division.

Staining Reactions: The spirochetes stained rather well with Fontana's stain (fig. 3) and moderately well with Wright's stain. The effectiveness of Wright's stain was increased by using slides previously treated with a film of brilliant cresyl blue.

Cultural Characteristics: The organisms grew best at 37 C. in 300 cc. flasks of dextrose-beef infusion broth containing a small amount of blood and ascitic fluid. The cultures were covered with melted petrolatum and the flasks placed in a jar containing carbon dioxide under 75 mm. pressure. No growth occurred at room temperature. Although anaerobic conditions were obligatory for initiating growth in blood cultures, subcultures under aerobic conditions yielded growth. Blood and ascitic fluid were necessary elements of the mediums in most instances, although on a few occasions the organisms were cultured in plain beef infusion broth.

The fusiform bacillus was usually the first form to appear in the cultures and was observed in cultures three to seven days old. A few days later short spirochetes appeared. During the next two weeks the spirochetal forms appeared to increase in length, breadth and number but to decrease in motility. The more numerous the spirochetes, the smaller the individual organism.

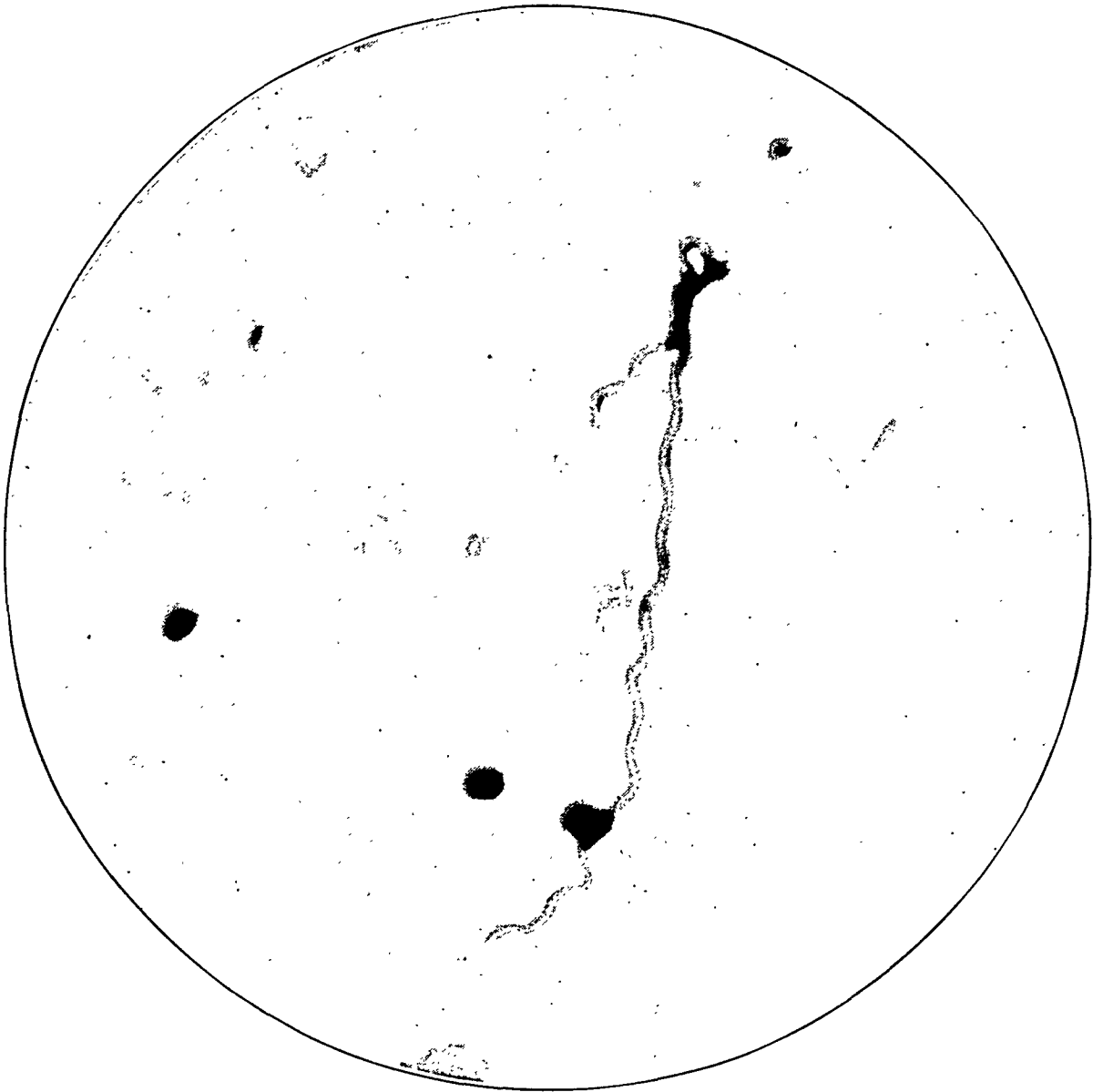


Fig. 5 (case 1).—Spirochetes ($\times 3,000$), stained by Fontana's method, in a blood culture.

After about four weeks most of the cultures acquired a putrid odor and exhibited gas formation. Cultures at this stage contained, in addition to fusiform bacilli and spirochetes, many short rods which were nonmotile, stained irregularly and, except for greater thickness, resembled diphtheroid bacilli. At this stage in two cultures many of the spirochetes gave the appearance of branching (fig. 6). Subcultures yielded only the diphtheroid form, which grew well aerobically on blood

agar slants. The colonies were grayish white and resembled those of *Staphylococcus albus*. The diphtheroid forms fermented dextrose rapidly with the production of gas, but fermentation and gas formation took place slowly with maltose, mannite, xylose, sucrose and lactose. These organisms may represent the type III fusiform bacillus described by Smith.⁵

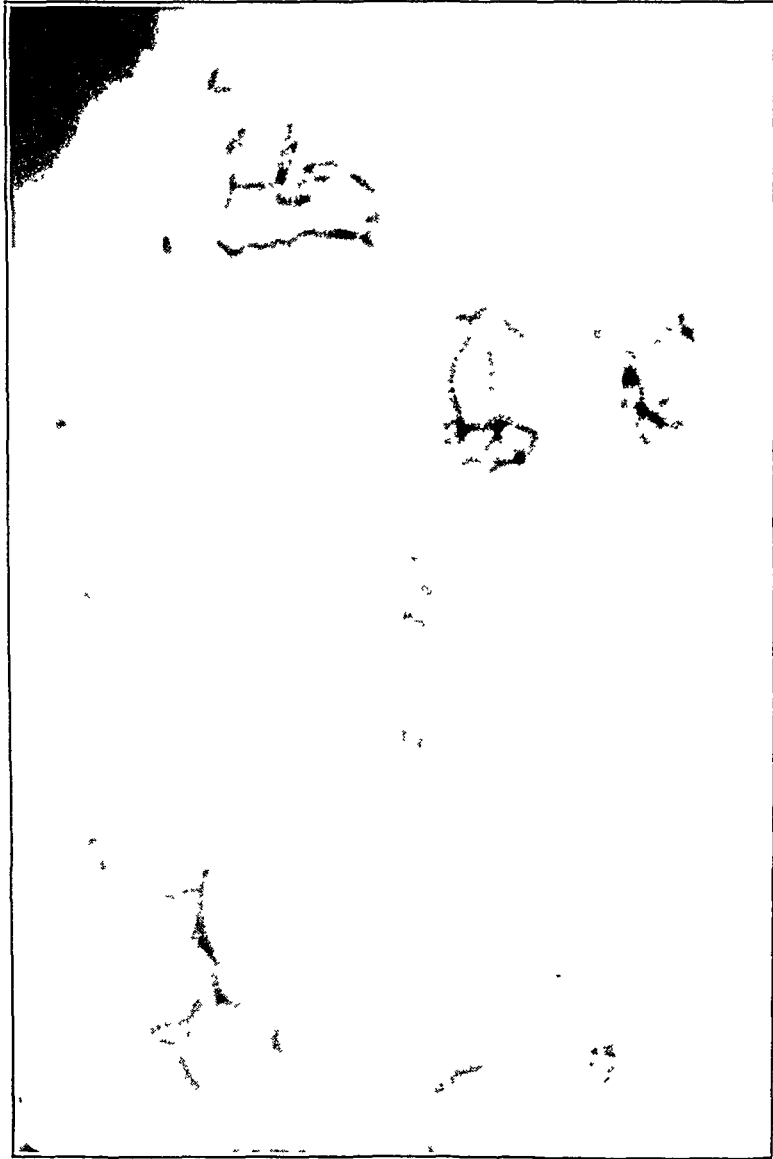


Fig. 6 (case 1).—Branching forms of spirochetes ($\times 2,000$), stained by Wright's method, in a blood culture.

Special Biochemical Reactions: Under the influence of tryptic digestion the spirochetes remained actively motile and unchanged for more than two days. In the presence of a 10 per cent solution of bile salts most of them were dissolved within two hours. With a 10 per cent solution of saponin they became immobile in one

5. Smith, D. T.: *Oral Spirochetes and Related Organisms in Fuso-Spirochetal Disease*, Baltimore, Williams & Wilkins Company, 1932.

hour and were partially dissolved in two hours. With distilled water they were motile at the end of two days and showed no plasmolysis.

Animal Inoculation: A large number of animals were inoculated in various sites with cultures and with the patient's blood. A *Macacus rhesus* monkey, mice, rats, guinea pigs and rabbits were employed. Some of the blood was collected in a solution of sodium citrate, and some was injected without an anticoagulant. The animals were observed for periods of five days to three months, and dark field examinations of the blood were made daily for the first two weeks following inoculation and several times a week thereafter. In many instances dark field examinations were made of material from the site of injection. The blood and other body fluids of the animals were cultured frequently. However, spirochetes or fusiform bacilli were rarely recovered. Many animals were killed and subjected to postmortem examination. No macroscopic lesions were observed, and microscopic examination of the viscera revealed no significant abnormalities. These negative observations may be summarized as follows: Samples of original blood cultures containing numerous motile spirochetes were inoculated as follows: (1) intraperitoneally into 5 rats, 4 guinea pigs, 2 mice and 1 *Macacus rhesus* monkey; (2) intravenously into 2 rabbits; (3) intratesticularly into 2 rabbits, and (4) subcutaneously into 2 rats, 2 guinea pigs and 2 rabbits. Although this experiment indicated, in the main, that the organisms possessed but little virulence for the species of animals used, certain other animal experiments are of possible significance and are worthy of record.

On July 15 a dark field examination was made of blood from a rabbit. No organisms were observed. A blood culture was also made, but it yielded no growth. Then the animal was inoculated intravenously with 10 cc. of patient E. D.'s blood in a solution of sodium citrate. Two days later a few spirochetes were observed in a dark field preparation of the rabbit's blood. However, the organisms could not be grown in culture, and, in spite of frequent dark field examination during the next two months, their presence in the blood could not be demonstrated again.

On July 29 a rat was inoculated intraperitoneally with 5 cc. of fresh whole blood from patient E. D. The rat died August 4. Dark field examinations of the heart blood and the peritoneal fluid revealed no spirochetes. However, in the peritoneal fluid many coarse granular structures were observed. Petrolatum was placed around the edges of the cover glass, and the slide was preserved at room temperature. The following morning a few motile spirochetes were observed. A week later postmortem cultures of the peritoneal fluid of this rat contained numerous motile spirochetes. Within another week the culture contained organisms of the same size and appearance as those in the cultures made directly with the patient's blood. The organisms from peritoneal fluid were subcultured successfully three times. A postmortem culture of the heart blood of the rat remained sterile.

On August 16 samples of blood from 4 rats were examined under dark field illumination and were cultured. No spirochetes were observed, and the cultures yielded no growth. The rats were inoculated intraperitoneally with a fourth subculture of the patient's blood. Dark field examinations of blood from these rats were made daily and were negative for spirochetes. Several cultures of the heart blood of 3 rats remained sterile; a culture of blood from the heart of rat 4, made August 19, was found to contain a few slender spirochetes two weeks later. A second culture, made August 24, also yielded spirochetes. The animal died September 2. No organisms were revealed by dark field examinations of the heart blood and the peritoneal fluid. Rat 1 died two weeks after inoculation. A dark field examination of the blood showed no organisms. In the peritoneal fluid there

were many motile spirochetes and motile rods. The spirochetes appeared morphologically similar to those in cultures of the patient's blood. Cultures were made of the rat peritoneal fluid, brain and heart blood. Motile spirochetes and rods were found after one week and were subcultured successfully, without difficulty. Rats 2 and 3 remained normal. They were killed four weeks after inoculation. Postmortem cultures and dark field examinations gave negative results.

On August 22 a rat which had been shown by a culture and a dark field examination of the blood not to have preexisting spirochetosis was inoculated intraperitoneally with 5 cc. of the patient's whole blood. No anticoagulant was employed. Frequent cultures and dark field examinations of the animal's blood revealed no organisms. Finally, a culture, made September 15, yielded spirochetes. No subcultures were made. The animal survived. Subsequent dark field examinations of the blood revealed no organisms.

Since it had been established that the patient had a gonococcic infection and undulant fever, it seemed important to determine whether experimental infection with the spirochetes obtained from his blood could be established more regularly in animals in the presence of another infectious agent. Three rats which had been shown previously to be free of spirochetes, by culture and dark field examination of the blood, were used. The animals were inoculated intraperitoneally with a broth suspension of gonococci to which had been added 0.5 cc. of culture of the spirochetes (obtained from the patient's blood). The animals were killed on September 22. Dark field examinations of the heart blood and peritoneal fluid revealed no organisms. Cultures of the blood and fluid from 2 of the rats remained sterile. On September 29 a culture of the heart blood of the third rat was found to contain spirochetes. These were transferred successfully through several generations.

CASE 2.—E. M., a white man aged 24, was admitted to the hospital June 27, 1938 complaining of pain and swelling about the left hip. He stated that he had felt well until four days previously, when chilliness developed, with fever, prostration, anorexia and nausea. Within a few hours severe pain in his head, arms, back and legs occurred. Three days later the left hip became swollen, red and painful. The following day these symptoms were more marked, and he came to the hospital.

At the age of 10 he fell off a pony and landed on the left hip. The injury did not seem severe at the time, but one year later it was noted that he favored this leg in walking.

One month before his admission to the hospital a rat bit him on one finger. The injury appeared trivial, and it healed within a few days, without apparent scar formation.

Five days before the onset of the febrile illness he had been working in a swamp and was bitten by many mosquitoes.

Physical Examination.—The temperature was 102.4 F., the pulse rate 88 and the respiratory rate 22. He was restless and complained of a great deal of pain about the left hip, but he did not appear to be seriously ill. He was not undernourished. The skin was normal. The cervical, axillary and inguinal nodes were slightly enlarged. The heart and lungs were normal. The spleen and liver were not felt. There were no abnormalities in the joints, except about the left hip. There were some atrophy of the muscles of the left hip and slight shortening of the left leg. The skin over the hip was red, hot and tender, and movements in the hip joint were painful.

Laboratory Data.—The urine was normal. The hemoglobin content was 13.2 Gm. per hundred cubic centimeters of blood, the red cell count 5,090,000 per cubic millimeter and the white cell count 11,300, with a normal differential count. The Kahn reaction of the blood was negative. Examination of a stool did not reveal blood, pus or parasites. Repeated examinations of prostatic secretion showed no gonococci. A thick smear of the blood was negative for the causative organisms of malaria. The patient's serum did not agglutinate any of the following organisms: *Bacillus typhosus*, *Bacillus paratyphosus* A and B, *B. abortus* and *B. melitensis*. The opsonocytophagic test for brucellosis showed no phagocytosis. The cutaneous test with brucellergen gave no reaction. The complement fixation test for gonococcic infection was negative. Two electrocardiograms were normal. A roentgenogram of the left hip exhibited changes interpreted as Legge's disease (osteochondritis deformans juvenilis).

Course.—In spite of frequent doses of acetylsalicylic acid and codeine sulfate, the pain in the left hip was so severe that the patient was given morphine sulfate on several occasions. Two unsuccessful attempts were made to aspirate fluid from the joint. For two weeks his temperature fluctuated between 101 and 103 F. Two days after the patient's admission to the hospital moderate swelling, redness, tenderness and increased heat developed about the proximal interphalangeal joint of the index finger on the left hand. The following day inflammation here had largely subsided, but the pain in the hip had increased. Two days later signs of acute inflammation of the left wrist developed and persisted for about twenty-four hours. Subsequently transitory pains occurred in the right ankle and right shoulder.

The patient's temperature gradually fell during the third and fourth weeks of his stay in the hospital. On July 25, approximately one month after his admission and after he had become free of fever, he received 0.6 Gm. of neoarsphenamine. The treatment was borne well, and he was given two subsequent injections before discharge on August 3. Two blood cultures were made between July 25 and August 3. Both remained sterile after long periods of incubation.

Bacteriologic Studies.—Dark field examinations of the patient's blood and urine were negative for spirochetes. Cultures of the urine yielded no growth. Cultures of the blood made June 28 and July 1 remained sterile. A third blood culture, made July 2, yielded spirochetes and fusiform bacilli after eleven days of incubation. The culture methods employed were the same as those described in case 1. The organisms observed in dark field preparation and in stained specimens appeared identical with those in case 1. The first subculture yielded good growth. Subsequent subcultures remained sterile. A sample of the original culture was inoculated intraperitoneally into a rat and a guinea pig. Dark field examination and cultures of the blood of these animals did not reveal spirochetes or fusiform bacilli. A sample of the patient's blood was collected in a solution of sodium citrate and inoculated intraperitoneally into a rat and a guinea pig and intravenously into a rabbit. No spirochetes or fusiform bacilli were found subsequently, in spite of frequent dark field examinations of specimens of blood from these animals.

COMMENT

The courses of the illness experienced by the 2 patients were similar in many respects. The initial symptoms of illness in both instances resembled those of rat bite fever, relapsing fever and Weil's disease. Fever suddenly developed, associated with chilliness, prostration, head-

ache and aching in muscles and joints and, subsequently, with migratory arthritis. The arthritis was accompanied by objective manifestations. The first patient, E. D., suffered from an intermittent type of arthritis for two years, whereas the second patient, E. M., was free of arthritic symptoms after one month. Over a period of two years E. D. experienced occasional bouts of fever, which varied in duration from a few days to several weeks. E. M. was observed early in the course of his infection and was febrile for five weeks. The subsequent course, after treatment, is unknown.

On physical examination both patients presented evidence of arthritis. In one, E. M., the manifestations were acute, and in the other, chronic, with acute exacerbations. There was slight enlargement of some of the superficial lymph nodes in both patients and of the spleen in one, E. D. In E. D., a hemorrhagic rash, slight jaundice and acute pleuritis also developed. In neither patient was the infection associated with anemia. There was never more than slight leukocytosis. Wassermann and Kahn reactions were negative. Spirochetes could not be demonstrated by direct examination of the blood, although they were cultured from the blood of the first patient eleven times and from that of the second patient once. They were not found in the urine of either patient.

On the basis of the criteria for the identification of spirochetes presented by Noguchi⁶ and by Hindle,⁷ it appears that the organisms which we recovered belong to the genus *Spirochaeta* and are the type encountered in Vincent's angina.

The main characteristics of the spirochetes which we recovered may be summarized. The average measurements, expressed in microns, were: length 15, width 0.6, spiral amplitude 3 and spiral depth 1.8. The number of spirals varied from two to thirty-five. The motion was usually corkscrew-like, but serpentine, earthworm-like and rotary movements were also observed. Fusiform bacilli of varying sizes were usually found with the spirochetes. The latter organisms readily took either Fontana's or Wright's stain. They grew well in dextrose-infusion broth containing ascitic fluid if the surface was covered with petrolatum and if they were incubated at 37 C. in a jar containing carbon dioxide. They usually grew out in a week and continued growing in the same culture for more than a month, producing a foul odor. Subcultures were made as many as nine times. The organisms were resistant to

6. Noguchi, H.: The Spirochetes, in Jordan, E. O., and Falk, I. S.: The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, pp. 452-597.

7. Hindle, E.: The Spirochetes, in Arkwright, J. A.; Bedson, S. P., and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1931, vol. 8, pp. 101-138.

tryptic digestion but were almost completely disintegrated and dissolved in the presence of a 10 per cent solution of bile salts or of saponin. They were mildly pathogenic for rats, 1 rat dying one week and 1 rat two weeks after intraperitoneal inoculation. The organisms were found in either the heart blood or the peritoneal fluid of 5 rats, sometimes by direct dark field examination and at other times by culture. They were observed about two weeks after the animals had been inoculated intraperitoneally. They were recovered either when the patient's blood or a culture of the blood was used as the inoculum. Successful subcultures were made repeatedly.

Both patients apparently were benefited by treatment with arsphenamine. Clinical improvement followed, and fusiform bacilli and spirochetes seemingly disappeared from the blood. The first patient seemed to have the equivalent of a Herxheimer reaction after the administration of neoarsphenamine. Fever therapy appeared to exert a similar effect.

The source of infection in patient E. D. was possibly the tonsils, since they had been the source of symptoms for years. It is known that tonsils often harbor fusiform bacilli and spirochetes. The rat bite is considered the source of infection in the second patient. Smith⁵ has found fusospirochetes in the mouths of rats.

It is difficult to evaluate the role of brucellosis and gonococcic infection in the first patient. It is possible that these infections may have operated as factors favoring fusospirochetal infection.

SUMMARY

The recovery of fusiform bacilli and spirochetes, of the type found in Vincent's angina, in cultures of the blood of 2 patients is recorded. Fusospirochetes were recovered eleven times from 1 patient and once from the other. Successful subcultures of the organism were made repeatedly. The organisms were slightly pathogenic for rats.

In the 2 patients fusospirochetemia was associated with an illness characterized by the sudden development of fever, prostration, headache, myalgia and migratory arthritis. In 1 patient splenomegaly developed, with jaundice, a hemorrhagic eruption and acute pleuritis. The source of infection is considered to be the tonsils in 1 instance and the bite of a rat in the other.

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CAUSE OF THE SO-CALLED SIDE ACHE THAT OCCURS IN NORMAL PERSONS

PERSONAL OBSERVATIONS

RICHARD B. CAPPS, M.D.

CHICAGO

The "side ache," or "stitch in the side," that occurs with exercise in normal persons is well known to layman and to physician alike. It was mentioned by Pliny the Elder and by Shakespeare. In spite of its frequent occurrence, it has received little attention in the medical literature. Explanations regarding its mechanism have been largely speculative. I have been able to find only four papers in which actual data concerning its nature have been recorded. Benjamin,¹ in 1923, stated that this pain occurred only in "constitutionally inferior children." He claimed that because of faulty vasomotor regulation, exercise resulted in congestion and swelling of the liver and the spleen. The pain was due to visceral distention and to pulling on the suspensory ligaments. He stated that relief was obtained by deep breathing, by tightening of a belt or by local external pressure. He detected enlargement of the liver and the spleen by percussion. In 1927 Herxheimer² carefully studied 42 children and young persons between the ages of 10 and 20 years. He concluded that pain was due to a pulling on the suspensory ligaments of the viscera caused by the bouncing or shaking which accompanies certain forms of exertion. He stated the belief that congestion did not play a role and found no evidence of visceral distention by roentgen or physical examination. According to his data, only walking, running or similar rhythmic bouncing exercise caused this pain. There was no relation to the amount of exertion. Bending over, local pressure or an abdominal binder gave relief. Nassau,³ in 1935, found that "perverted respiration" was present in patients who had this pain. By this he meant that during inspiration the abdomen relaxes so that there is no increase in intra-abdominal pressure, such as he said normally occurs. Thus, there results a stagnation

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1. Benjamin, K.: Zur Pathogenese der Wachstumsblässe, *Jahrb. f. Kinderh.* **102**:203, 1923.

2. Herxheimer, H.: Ueber das "Seitenstechen," *Deutsche med. Wchnschr.* **53**: 1130, 1927.

3. Nassau, E.: Ueber das sogenannte "Seitenstechen" der Kinder, *Klin. Wchnschr.* **14**:1252, 1935.

of blood in the abdomen with consequent congestion and distention of the viscera. His patients all were of the ptotic body type. Improved respiration resulted in disappearance of the pain. Kugelmass,⁴ in 1937, confirmed these findings. Both the last two authors obtained information in the main by asking children to recall their symptoms. Only Herxheimer presented data regarding actual observations on the pain.

A number of other causes have been suggested in the literature. Painful contraction of the spleen was blamed by Bancroft,⁵ Mosse⁶ and Rautmann.⁷ Painful distention of the spleen was suggested by Mosler⁸ and R. Schmidt.⁹ F. A. Schmidt¹⁰ mentioned pulling on the visceral suspensory ligaments and on the diaphragm. Finally, Pembrey¹¹ expressed the opinion that spasm of the intercostal muscles was the cause.

Because of the diverse views concerning this phenomenon, and especially because of the relative lack of accurate firsthand information regarding its characteristics, it seemed desirable to reinvestigate the problem.

MATERIAL

Personal observations were made over a period of several years on different groups of persons subject to this pain. By watching the track team of the University of Chicago High School through their winter track season I noted many cases. A few college track men were seen during the same period. Men out of training were observed in an impromptu professional-school track meet at the downtown campus of Northwestern University and likewise in an interfraternity turkey race among college students in Evanston, Ill. Cases were also seen among students engaging in other sports, such as wrestling and basketball, through the coaching staff at Northwestern University. A number of cases were noted and carefully observed among friends. A few examples were found among patients. Finally, interesting data were obtained from a number of professional coaches.

RESULTS

General Data.—One hundred and fourteen attacks of so-called side ache were personally observed in 55 different persons. Forty-four of

4. Kugelmass, I. N.: The Respiratory Basis of Periodic Subcostal Pain in Children, *Am. J. M. Sc.* **194**:376, 1937.

5. Bancroft, J.: Die Stellung der Milz im Kreislaufsystem, *Ergebn. d. Physiol.* **25**:818, 1926.

6. Moses, M.: Milzstiche, *Med. Welt* **1**:17, 1927.

7. Rautmann, H. L.: Ertrinkungstod und Wiederbelebung, *Med. Welt* **1**:1047, 1927.

8. Mosler, F.: Krankheiten der Milz, in von Ziemssens, H.: *Handbuch der speciellen Pathologie und Therapie*, ed. 2, Leipzig, F. C. W. Vogel, 1878, vol. 8, pt. 2, pp. 1-196.

9. Schmidt, R., cited by Herxheimer.²

10. Schmidt, F. A.: *Unser Körper*, Leipzig, Voigtländer, 1929.

11. Pembrey, cited by Kugelmass.⁴

the subjects were males and 11 were females. The ages ranged from 15 to 65 years, but only 3 were over 35 years of age. Twenty-five of the subjects were seen in more than one attack. All subjects were normal and healthy as far as is known. In several instances a similar pain was observed in diseased persons, but data from these persons were not included in the tables. They are mentioned in the section entitled "Comment." Complete information was, unfortunately, not obtained in every case, so that only definite and reliable data are included.

Location of Pain.—The frequency of the various sites of pain can be seen in table 1. The right or left upper quadrant of the abdomen was the usual location. The 3 subjects with precordial pain and pain in the second left costal interspace had just finished a mile (1.6 kilometers) run and were completely exhausted. This may represent a different type of

TABLE 1.—*Location of Pain in Individual Attacks*

Sites of Pain for Entire Series			
Right upper quadrant of abdomen....	51	Right nipple.....	2
Left upper quadrant of abdomen....	33	Right median part of abdomen.....	2
Epigastrium.....	6	Substernal area.....	2
Left median part of abdomen.....	5	Left costal margin.....	1
Right costal margin.....	4	Navel.....	1
Left lower quadrant of abdomen....	3	Left second interspace.....	1
Precordium.....	2	Right and left upper quadrants of abdomen..	1
Location of Pain in Persons with Two or More Attacks			
Pain always on same side.....			7
Pain on different sides.....			18
Location of Pain in Strenuous Exertion and in Mild Exertion			
Same location.....			4
Different locations.....			8
Persons who had pain only with one type of exertion.....			13
Same location.....			9
Different locations.....			13

pain from the ordinary side ache. It should be noted that the site of pain was often not constant in the same person on different occasions. This was true even though the type of exertion was the same. It is noteworthy that shoulder pain was never observed, although it was specifically looked for.

Character of Pain.—The character of the pain was variable. It was described as sharp in 37 cases and as dull in 10. In 2 instances, both of substernal pain, it was constricting. In 1 instance each the sensation was said to be that of pressure, of a cramp and of gnawing. The pain usually lasted only a few minutes, although occasionally it lasted ten to twenty minutes. Tenderness was noted in the region of pain in 8 cases, while in 11 there was no tenderness.

Precipitating Factors.—Physical exertion of some kind was always the chief precipitating factor. Simple twisting or bending of the body alone was never observed to cause this pain. The requisite type of

exercise varied from walking to strenuous running, including both sprints and the longer distances, up to 2 miles (3.2 kilometers). Other forms of exertion, such as horseback riding, swimming, boxing, wrestling, skiing, squash and basketball, were also observed to be adequate cause in individual cases. Although not specifically tested, the amount of exercise required to produce pain in a given person under similar circumstances seemed to be relatively constant.

As seen from table 2, mild exercise, such as walking, was effective in producing a side ache usually only when indulged in soon after a meal. In 4 of the 11 women pain was more likely to occur at the time of menstruation. No correlation was found between the severity or type of exertion and the location or character of the pain. As is seen in table 1, in 4 persons who had pain with both mild and strenuous exercise the pain was in the same location, whereas in 8 others it occurred in different locations. On the other hand, in 9 subjects who

TABLE 2.—*Precipitating Factors**

Strenuous exertion.....	51	
Strenuous exertion post cibum.....	3	
Total.....	—	54
Mild exertion.....	16	
Mild exertion post cibum.....	44	
Total.....	—	60
Effect of Training		
Pain disappeared with training.....	2	
Pain failed to disappear with training.....	3	

* Figures represent individual attacks.

had pain on several occasions the pain experienced during the same type of activity was in the same location, whereas in 13 others it was in different locations.

The effect of physical training was also variable. In 2 persons the side ache definitely disappeared with training, and in 3 others it continued to be present despite excellent training. This variability was confirmed by several coaches, who agreed that in some persons the pain was only present when the physical condition was poor or when the person was "warming up." And yet in other cases no matter how excellent the training, the pain persisted. In some persons it is so severe that nausea and vomiting ensue. Although in a few cases the pain may disappear even though the exertion is continued, this is not usually so. Thus there seems to be no definite relationship to the "second wind."

Cold weather was reported to be a factor by one coach. He described an intercollegiate cross country track meet in which 40 out of 60 competitors were forced to stop and be driven back because of the severity of the side ache. The temperature was around 15 F. In another

instance a cross country team "warmed up" outside in severe cold and were all able to complete the race. The opposing team "warmed up" inside the field house, and all but 1 were forced to drop out of the race because of stitch pain.

Respiration.—Deep breathing increased the pain in 25 instances, had no effect in 33 and gave relief in 3. In 53 attacks this feature was not noted.

Factors Giving Relief.—These are recorded in table 3. It should be noted that either bending over, usually toward the affected side, or pressure with the hand over the painful abdominal region, or both, gave relief in 42 instances. The effect of these maneuvers was, unfortunately, not investigated in the remainder of the subjects. In only 4 instances was bending over found to be ineffective. Tightening of a belt was said by one coach to be of value in enabling some athletes to control the pain and to continue their endeavors. In several carefully observed subjects, bending over stopped the pain though exercise was continued. This

TABLE 3.—*Factors Giving Relief* *

Bending over (failed in 4).....	28
Pressure.....	14
Stopping exertion.....	32
Holding breath.....	3
Deep breathing.....	3
Loosening belt.....	3

* The figures represent individual attacks. It is to be noted that bending and/or pressure relieved 42 attacks. Of these, 21 were from mild exertion and 11 were from strenuous exertion.

observation was repeated several times. Bending over was found to relieve the pain produced by both mild and strenuous exertion.

COMMENT

The outstanding features of the stitch pain are its relation to exertion, its tendency to occur after eating, its variable location even in the same person in the right or the left upper quadrant of the abdomen and the relief obtained from bending or pressure. These observations are in general confirmed in the literature. The relation to respiration is indefinite, although I found that the pain was often relieved by deep breathing. This is at variance with the observations of Nassau³ and of Kugelmass.⁴ Finally, cold weather appears to be a previously unrecognized predisposing factor. A satisfactory explanation of the mechanism of this pain must take all of these factors into account.

From a consideration of the foregoing data it becomes clear that certain of the proposed theories are obviously untenable. Painful contraction of the spleen¹² fails to explain pain on the right side. Spasm

12.—Bancroft.⁵ Mosse.⁶ Rautmann.⁷

of the intercostal muscles¹¹ should produce pain over the muscles involved. Furthermore, this hypothesis is not supported by any direct evidence. The pain could hardly be due to pulling on the suspensory ligaments of the viscera, as proposed by Herxheimer,² for I have repeatedly observed its appearance during such activities as swimming, skiing and wrestling, in which rhythmic bouncing does not occur to any extent. Also, I have observed a relationship between the appearance of the pain and the extent of the exertion. Certain other possibilities which might come to mind, such as spasm of the intestine and spasm of the abdominal muscles, obviously fail to satisfy the criteria.

The last, and perhaps most generally held, theory is that of congestion and distention of abdominal viscera, due to the heart, to abnormal vasomotor reactions¹ or to faulty respiration.¹³ First, it appears unlikely that visceral distention from whatever cause can satisfactorily explain the side ache. Since the pain is usually well to the side, the liver and spleen must be the chief organs involved. It seems unlikely that the splenic and hepatic flexures of the colon would be involved without the rest of the intestine; and, except for these points, intestinal pain should be mostly in the midline.¹⁴ Painful distention of the spleen in clinical conditions associated with venous congestion is certainly unusual and could hardly be expected in the absence of a similar situation in the liver. Herxheimer,² in careful studies, including roentgen and physical examinations, found no evidence for enlargement of the liver or the spleen. Furthermore, tenderness, which is nearly always present in the pathologically congested liver, is not a prominent feature of the side ache. Finally, exertion should tend to cause splenic contraction.⁵ I have observed a man with mild congestive failure and an enlarged liver who had what was comparable to a stitch pain on exertion, but only in the right upper quadrant of the abdomen. There was marked local tenderness over the liver.

Second, in regard to the presence of abnormal vasomotor reaction or faulty respiration, I can only state that the subjects were not of any single body type. It is common knowledge that the incidence of the stitch pain is so high that it could hardly be limited to those with the ptotic body type. In contradistinction to Nassau and Kugelmass, I found that deep breathing usually increased the pain rather than gave relief. Although they claimed that breathing exercises prevent the attacks, one is not justified in concluding that abnormal respirations cause visceral distention. Their observations are susceptible of a different interpretation; namely, a change in breathing habits might simply

13. Nassau.³ Kugelmass.⁴

14. Jones, C. M.: *Digestive Tract Pain*, New York, The Macmillan Company, 1938.

alter the load on the diaphragm. Finally, acute heart failure is readily eliminated as a probable factor, since relatively mild exercise in trained athletes may precipitate the pain.

It is thus evident that none of the previously proposed explanations of this pain are satisfactory. There is another possible cause that, so far as I know, has never been suggested, namely, anoxemia of the diaphragm. This explanation, which was first suggested to me by Dr. George H. Coleman, satisfies, I believe, all of the requirements in a much more satisfactory manner than any other.

The reference of pain from the muscular portion of the diaphragm is not definitely established. Gill and McArdle¹⁵ reported 2 cases of hysteric spasm of the diaphragm without pain. Porter¹⁶ described a case and reviewed the literature of diaphragmatic flutter with distribution of pain like that in angina pectoris. The consensus is that the pain in such cases arises in organs other than the diaphragm and is brought about only by reflexes arising from abnormal diaphragmatic action. These observations throw little light on the distribution of pain referred from the diaphragmatic muscle. It is known, however, that the pleura and peritoneum which overlie the muscular portion of the diaphragm refer pain to the lower intercostal nerves.¹⁷ It is not unreasonable to suppose that these same fibers may refer pain from the underlying muscle. Furthermore, the blood supply of the diaphragm is intimately associated with the intercostal arteries, and afferent vegetative fibers running with the vasomotor nerves might well refer pain to the intercostal nerves connecting with the same or an adjacent spinal segment. This distribution of pain corresponds closely to that observed in the stitch.

Actual physical exertion is obviously necessary to produce anoxemia, and this might vary with the physical condition of the subject, with the type of breathing, with the state of being "warmed up" and with the postprandial condition. Cold weather would be expected to affect the diaphragm much as it does the heart in cases of angina pectoris or the leg muscles in cases of intermittent claudication. This also holds true of eating. Deep breathing would be expected to increase the pain, as it was frequently found to do. Holding the breath, although it stops diaphragmatic contractions, also increases anoxia, so that it would have variable effects. Bending over, especially toward the affected side, and local pressure both act to limit diaphragmatic motion and so would be

15. Gill, W. G., and McArdle, M. J.: Two Cases of Pseudo-Tympanites Caused by Hysterical Spasm of the Diaphragm, *Guy's Hosp. Rep.* **84**:94, 1934.

16. Porter, W. B.: Diaphragmatic Flutter with Symptoms of Angina Pectoris, *J. A. M. A.* **106**:992 (March 21) 1936.

17. Capps, J. A.: An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum, New York, The Macmillan Company, 1932.

expected to give relief of stitch pain, even though physical exertion were continued. This effect on diaphragmatic motion of bending over has been confirmed by Dr. Hollis E. Potter¹⁸ by actual observation of the diaphragm under the fluoroscope. One other observation also offers strong corroborative evidence. I have frequently observed both in myself and in others a pain in every way identical with the side ache which is brought on by strenuous and prolonged laughter, especially after a large meal. Laughing is accompanied by a series of rapid contractions of the diaphragm, often without adequate respirations. Possibly in excessive laughter there is a spasm of the diaphragm, as it may become difficult to draw a deep breath. Such a pain is probably identical with the side ache of exercise in that it arises from the diaphragmatic muscle. Perhaps this is the origin of the term "side-splitting" laughter.

Why the pain is generally unilateral is not entirely clear. It is natural that one side should be affected first, and perhaps the person stops exercising before the other side begins to hurt. Finally, it should be pointed out again that the observations of Nassau and Kugelmass are on the whole consistent with this explanation of the mechanism of the pain. Improved breathing might well put less of a load on the diaphragm.

SUMMARY

1. One hundred and fourteen attacks of side ache occurring in 55 persons have been personally observed and the important features analyzed.

2. The outstanding characteristics are found to be a constant relation to exertion, a tendency to occur after eating, a variable location, usually in either the right or the left upper quadrant of the abdomen, relief obtained from bending over or from local pressure and a tendency to be aggravated in cold weather.

3. The previously proposed theories regarding the mechanism of pain are shown to be untenable. A new explanation of the pain is suggested, namely, anoxemia of the diaphragmatic muscle. This theory explains all of the observed facts in an entirely satisfactory manner.

Assistance was given by the coaches and athletic directors at the University of Chicago High School, the University of Chicago and Northwestern University.

18. Potter, H. E.: Personal communication to the author.

VITAMIN A AND CAROTENE CONTENT OF HUMAN LIVER IN NORMAL AND IN DISEASED SUBJECTS

AN ANALYSIS OF ONE HUNDRED AND SIXTEEN HUMAN LIVERS

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The vitamin A content of the liver has been reported by several observers,¹ but as a variety of methods were used for the determination of vitamin A and as many of these methods have since been shown to have a wide margin of error, the majority of the results are qualitative rather than quantitative. An exception to this is the report by Crimm and Short,² in which the livers of 7 healthy persons were found to have an average vitamin A content of 33,100 U. S. P. units per hundred grams of liver. In a later study³ they reported that in 50 patients with tuberculosis the average vitamin A content of the liver was 34,200 U. S. P. XI units per hundred grams. In 14 of the patients, however, the vitamin A content of the liver was low. Occasional scattered reports of both the vitamin A and the carotene contents of human livers may be found,⁴ but there are no large series of cases in which the concentrations of these two substances in human livers have been observed. As the source of vitamin A in the diet under ordinary circumstances is carotene, which

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1. Moore, T.: Distribution of Vitamin A and Carotene in the Body of the Rat, *Biochem. J.* **25**:274, 1931; Vitamin A Reserves of Human Liver in Health and Disease, *Lancet* **2**:669, 1932. Fox, F. W.: Vitamin A in Livers of Native Miners, *ibid.* **1**:953, 1933. Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, *ibid.* **2**:617, 1932.

2. Crimm, P. D., and Short, D. M.: Vitamin A Content of Human Liver, *Am. J. M. Sc.* **189**:571, 1935.

3. Crimm, P. D., and Short, D. M.: Vitamin A Content of the Human Liver in Tuberculosis, *Ann. Int. Med.* **13**:61, 1939.

4. Pariente, A. C.; Present, C. H., and Ralli, E. P.: A Case of Carotenemia and Diabetes Mellitus with Necropsy Report and Analyses of Liver for Carotene, Vitamin A, Total Fat and Cholesterol, *Am. J. M. Sc.* **192**:365, 1936. Flaum, G., and Stueck, G. H., Jr.: Hemochromatosis: Report of a Case with Necropsy and Analysis of the Liver, *Arch. Int. Med.* **63**:433 (March) 1939.

must be converted by the liver to vitamin A before it is utilized by the body, it seemed to us that the concentration of these two substances in the liver and their relationship to each other were of interest.

In this study the livers of 116 persons were analyzed. The material was obtained at autopsy.⁵ Twenty-five of the subjects were healthy persons who were killed in accidents. The remaining 91 suffered from various diseases and are divided into groups according to the clinical diagnoses and pathologic findings. Vitamin A was determined after extraction⁶ in the Hilger vitameter. Carotene was determined on the same extract in the photoelectric colorimeter.⁷ Samples of the liver were obtained in most cases within twenty-four hours after death.

RESULTS OF ANALYSIS

GROUP I: *No Disease* (25 subjects; table 1).—The material in this group was derived from persons who had been killed in accidents and in whom no gross pathologic condition was observed at autopsy except the immediate cause of death. Of these persons, 20 were males and 5 were females. The ages varied from 4 to 81 years.

The average vitamin A content of the liver of these normal subjects was 121,000 U.S.P. units per hundred grams of wet liver. There was a considerable range, as can be seen in the table, but in 18 of the normal subjects the vitamin A content of the liver was above 40,000 U. S. P. units per hundred grams and in 8 it was above 100,000 U.S.P. units. The average vitamin A content of the liver in this series of normal subjects is four times as high as the average value reported by Crimm and Short (33,100 U. S. P. units per hundred grams of liver). As 18 of the normal livers in our series had a vitamin A concentration above 40,000 U. S. P. units per hundred grams of liver and as Crimm and Short analyzed only 7 normal livers, it seems to us that the value they obtained is at the lower level of normal. As will be seen in the other tables, in many of the livers of the patients with disease the amount of vitamin A was appreciably reduced. The lowest vitamin A content of the liver in this normal group was that for patient 100 (3,400 U. S. P. units), in whom both the vitamin and the carotene were so low as to suggest a low dietary intake.

5. The samples of liver were obtained for analysis through Dr. Douglas Symmers, director of the department of pathology of Bellevue Hospital, and through the Department of Hospitals and the office of the Chief Medical Examiner, New York.

6. Davies, A. W.: The Colorimetric Determination of Vitamin A by the Alkali Digestion Method, *Biochem. J.* **27**:1770, 1933.

7. Stueck, G. H., and Ralli, E. P.: The Application of the Photoelectric Colorimeter to the Determination of Carotene in Blood Serum, Liver and Feces, *Am. J. Physiol.* **119**:411, 1937.

The average carotene content of the normal livers was 1.44 mg. per hundred grams of wet liver. The range was from 0.33 to 3.71 mg. per hundred grams. The latter value, which is high, was found in the case of a 4 year old child and was accompanied by an unusually high concentration of vitamin A, undoubtedly reflecting a high dietary intake of carotene. The difference in the proportion of carotene to vitamin A may be due to the fact that in the infant the liver may not convert carotene as rapidly to vitamin A as does the liver in the adult. Clausen⁸ has shown that carotenemia is not at all uncommon in young children,

TABLE 1.—*Analysis of Livers from Twenty-Five Persons Without Gross Pathologic Conditions*

Case No.	Nutritional State of Subject	Age	Sex	Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A Carotene $\times 10^{-3}$
8	Fair	50	M	1,500	177,900	2.30	77
12	Fair	30	M	1,250	79,700	1.60	50
15	Good	10	M	950	130,000	1.40	93
16	Good	74	F	1,200	43,700	1.37	38
17	Good	35	M	1,300	197,800	1.20	165
4	Good	34	M	1,760	44,400	3.90	11
35	Good	45	M	1,630	95,500	1.96	48
47	Fair	30	M	1,820	72,900	0.43	169
49	Good	55	M	1,800	13,700	2.37	6
50	Good	40	M	1,670	23,600	0.97	24
69	Good	59	F	1,370	39,100	1.46	27
60	Good	55	M	1,780	46,200	0.45	103
61	Good	18	F	1,200	60,000	1.21	49
63	Good	14	M	1,100	60,400	1.32	46
71	Good	62	M	1,500	77,300	0.50	155
72	Good	55	M	1,620	234,200	0.91	257
76	Good	4	M	530	635,000	3.71	171
77	Good	35	F	1,170	55,900	1.64	34
80	Fair	39	M	1,500	114,000	2.52	45
81	Good	49	M	1,450	639,000	0.97	659
85	Good	35	M	1,650	16,900	0.35	48
89	Fair	45	M	1,470	25,200	0.33	76
90	Fair	81	M	1,410	134,900	1.56	86
94	Good	50	M	1,540	13,300	1.28	104
100	Fair	39	F	1,300	3,400	0.41	8
Average.....		42	..	1,430	121,000	1.44	84

and the increase in the blood may reflect an accumulation in the liver. The only other subject with as large a concentration of vitamin A in the liver was a 49 year old man (case 81), but the amount of carotene in the liver of this subject was 0.97 mg. per hundred grams of liver, which value indicates that in the normal adult liver the tendency is for carotene to be converted to vitamin A and to be stored as such. The proportion of vitamin A to carotene in the liver was calculated in an effort to determine whether these two substances bore any consistent relation to each other. The range of the ratio was large, with an average of 84×10^{-3} . Any significance that can be attached to this ratio is a

8. Clausen, S. W.: Limits in Anti-Infective Value of Pro-Vitamin A (Carotene), J. A. M. A. **101**:1384 (Oct. 28) 1933.

relative one and is brought out by comparing the ratio for the groups of diseased patients with that for the group of normal persons (table 5). Although in all of the former groups there is less vitamin A in proportion to the amount of carotene, when the ratios are compared the value for E shows that the difference is significant only for the group of patients with cirrhotic livers.

TABLE 2.—*Analysis of the Livers from Twenty-Six Patients with Acute and Chronic Alcoholism*

Case No.	Nutritional State of Patient	Age	Sex	Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A Carotene $\times 10^{-3}$	Pathologic Changes in the Liver and Other Disease Processes
56	Poor	35	F	2,450	7,800	0.23	34	Fatty liver; streptococcic meningitis
99	Good	35	M	1,780	15,000	1.24	12	Fatty liver
75	Poor	41	M	1,910	31,000	0.43	72	Lobar pneumonia; fatty liver
65	Good	40	F	1,750	21,600	2.26	9	Fatty liver
96	Good	45	M	1,450	47,100	0.38	129	Normal liver
82	Good	45	M	1,720	47,500	0.85	56	Pulmonary tuberculosis; fatty liver
66	Poor	50	M	1,410	146,000	2.23	65	Cardiac failure; normal liver
91	Fair	50	M	1,050	163,000	3.72	49	Slightly fatty liver
84	Good	38	M	1,850	31,300	0.77	41	Pulmonary tuberculosis
1	Good	..	M	2,350	58,300	1.80	32	Enlarged and fatty liver
25	Poor	68	F	1,450	35,700	0.40	89	Chronic passive congestion of liver; coronary thrombosis; ascites
28	Fair	50	M	1,800	47,100	0.64	74	Subdural hematoma
43	Good	..	F	1,500	31,900	0.60	53	
6	Fair	53	M	1,500	44,400	1.70	26	Coronary sclerosis
101	Fair	51	M	1,650	18,000	0.90	20	Fractured skull; cirrhosis of liver
102	Good	47	M	1,750	74,300	0.75	99	Enlarged heart, chronic passive congestion of liver
103	Poor	55	M	2,550	56,800	0.15	379	Hypernephroma; no metastases into liver
58	Poor	50	M	1,950	13,900	1.32	10	Pneumonia; cirrhosis
110	Good	47	M	4,000	900	0.07	13	Fatty liver; ascites; jaundice; cirrhosis
111	Fair	47	M	2,950	53,800	1.07	50	Fatty liver; ascites; jaundice; cirrhosis
113	Poor	39	M	3,500	5,300	0.00	5	Hemochromatosis; diabetes; ascites; cirrhosis
112	Poor	65	M	1,450	4,600	0.14	33	Portal cirrhosis; ascites
114	Poor	49	F	1,600	8,700	0.75	12	Cirrhosis; ascites; jaundice
115	Poor	24	F	1,700	0	0.58	0	Cirrhosis; ascites; jaundice
116	Poor	39	F	1,150	6,300	0.41	15	Cirrhosis; pulmonary tuberculosis; ascites; jaundice
39	Fair	62	M	3,300	4,900	0.05	98	Fatty liver; periportal fibrosis; cirrhosis
Average.....				1,980	37,500	0.90	57	

GROUP II: *Alcoholism* (26 patients; table 2).—This group consists of patients with a history of chronic alcoholism, some of whom were in a state of acute alcoholism when admitted to the hospital. In many of these patients other diseases, not directly the result of alcoholism, were also found, as is indicated in the table. Five of the patients were deeply jaundiced and had ascites. Ascites was also present in 3 other patients. There were 10 patients in whom cirrhosis of the liver was noted. In 12 patients the liver weighed more than 1,750 Gm.

In 16 patients the vitamin A concentration of the liver was below 40,000 U. S. P. units per hundred grams of liver, and in 9 of these it was below 15,000 U. S. P. units. The average for the group was 37,500 U. S. P. units per hundred grams of liver, which is the low limit of normal if both our results and those of Crimm and Short are considered. Although the average carotene value for this group was only slightly lower than that for the normal one, when it is considered in relation to the vitamin A value for the normal group the ratio is two-thirds that for the normal group. The low vitamin A content of the liver of these

TABLE 3.—*Analysis of the Livers from Fifteen Patients with Cirrhosis of the Liver*

Case No.	Nutritional State of Patient	Age	Sex	Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A Carotene $\times 10^{-3}$	Pathologic Changes in the Liver and Other Disease Processes
58	Poor	50	M	1,950	13,900	1.32	10	Alcoholism; lobar pneumonia; fatty liver; cirrhosis
39	Fair	62	M	3,300	4,900	0.05	98	Alcoholism; fatty liver; cirrhosis
13	Good	82	M	1,300	39,700	0.90	44	Arteriosclerotic heart disease; cirrhosis
31	Good	38	M	1,650	16,900	0.92	18	Lobar pneumonia; fatty liver; cirrhosis
98	Good	65	M	1,600	13,900	0.76	18	Cardiac failure; chronic passive congestion and cirrhosis of liver
38	Good	55	F	8,200	Cirrhosis of liver
101	Fair	51	M	1,650	18,000	0.90	20	Alcoholism; fractured skull; cirrhosis
106	Poor	26	F	1,880	10,700	0.15	71	Cardiac failure; cirrhosis
110	Good	47	M	4,000	900	0.07	13	Fatty liver; alcoholism; ascites; jaundice; cirrhosis
113	Poor	39	M	3,500	5,300	0.00	..	Alcoholism; hemochromatosis; ascites; cirrhosis
111	Fair	47	M	2,950	53,800	1.07	50	Alcoholism; fatty liver; jaundice; ascites; cirrhosis
112	Fair	65	M	1,450	4,600	0.14	33	Alcoholism; ascites; cirrhosis
114	Poor	49	F	1,630	8,700	0.75	12	Cirrhosis; alcoholism; ascites; jaundice
115	Poor	24	F	1,700	0	0.53	0	Cirrhosis; alcoholism; ascites; jaundice
116	Poor	39	F	1,150	6,300	0.41	15	Cirrhosis; pulmonary tuberculosis; alcoholism; ascites; jaundice
Average.....				2,120	13,700	0.57	31	

patients with alcoholism probably is due both to an inadequate dietary intake and to some hepatic dysfunction resulting either from the accumulation of fat in the liver or from cirrhosis. The factor which would be most likely to interfere with the storage of vitamin A or with the conversion of carotene to vitamin A would be some pathologic change in the liver, such as cirrhosis.

GROUP III: *Cirrhosis of the Liver* (15 patients; table 3).—In this table we have grouped the patients with cirrhosis of the liver. Ten of the 15 patients had a history of alcoholism. In 7 patients ascites was present. The livers were fatty in 5 patients, 4 of whom had a history of alcoholism.

The vitamin A content of the liver was strikingly lowered in all but 2 cases in this group, and in 1 of these the cirrhosis was described after microscopic examination as early. In the 13 remaining cases the vitamin A content was 18,000 U. S. P. units per hundred grams or below. The carotene value for the group was also lower than normal, and the carotene/vitamin A ratio averaged 31×10^{-3} , which when compared with the ratio for the normal group gave a significant value for E of 4.4. Both the lowered content of vitamin A in the liver and the decrease in the proportion of carotene to vitamin A point to the importance of normal hepatic tissue in the storage and the metabolism of these substances. As was mentioned before, with the destruction of normal hepatic cells the ability to store vitamin A is reduced and the conversion of carotene to vitamin A is interfered with.

TABLE 4.—*Summary of Results of Analyses of Livers from Normal Persons and from Patients with Various Diseases*

Disease	Number of Livers Analyzed	Average Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A Carotene $\times 10^{-3}$
None.....	25	1,430	121,000	1.44	84
Alcoholism.....	26	1,980	37,500	0.90	57
Cirrhosis.....	15	2,120	13,700	0.57	31
Acute infections without pathologic condition of the liver.....	16	1,760	45,400	0.95	63
Acute infections with pathologic condition of the liver.....	6	1,835	24,600	0.58	61
Chronic infections.....	10	1,760	38,300	0.79	59
Metabolic diseases.....	12	1,740	72,300	1.35	54
Malignant conditions.....	7	1,780	74,900	1.32	57
Cardiovascular diseases.....	16	1,540	53,300	1.37	43

GROUP IV: *Acute Infections* (22 patients; table 4).—This group consists of patients in whom the cause of death was an acute infectious process. In 16 of the patients there was no associated cirrhosis or fatty infiltration of the liver. The vitamin A content of the liver was below 40,000 U. S. P. units per hundred grams of liver in 8 of the 16 patients, and the carotene content was lower than normal. The ratio of vitamin A to carotene was 63×10^{-3} . The vitamin A content was below 40,000 U. S. P. units per hundred grams of liver in 5 of the 6 patients with cirrhosis or fatty infiltration of the liver, and the carotene was also reduced. The ratio of vitamin A to carotene was 62×10^{-3} for the entire group and thus again showed less vitamin A in proportion to the amount of carotene than is found in the normal liver.

GROUP V: *Chronic Infectious Diseases* (10 patients; table 4).—This group consists of patients dying of chronic infectious diseases. In 6 patients in this group the total vitamin A content of the liver was below

40,000 U. S. P. units per hundred grams of liver, and there was a corresponding reduction in the carotene content of the liver. The average carotene value for the group was 0.79 mg. per hundred grams of liver, with a range from 0.21 to 1.64 mg. These figures are at the lower limits of normal.

GROUP VI: *Metabolic Diseases* (12 patients; table 4).—This group consists of 8 patients with obesity which was complicated by some other pathologic process, 3 patients with diabetes mellitus and 1 patient with Paget's disease of the bones.

The vitamin A content of the liver was below 30,000 U. S. P. units in 3 of the obese patients, and in 2 of them the obesity was complicated

TABLE 5.—*Statistical Analysis*

Group	Disease	Vitamin A, U. S. P. Units per 100 Gm. of Liver		Carotene, Mg. per 100 Gm. of Liver		Vitamin A Carotene $\times 16^{-3}$	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
I	None.....	76,600	$\pm 62,500$	1.36	± 0.87	74	± 32.0
II	Alcoholism.....	37,500	$\pm 40,300$	0.90	± 0.91	57	± 74.0
III	Cirrhosis.....	13,700	$\pm 14,500$	0.57	± 0.49	31	± 28.8
IV	Chronic infection.....	38,300	$\pm 16,000$	0.79	± 0.44	59	± 46.3
V	Acute infection						
	(a) Without damage to the liver.....	45,400	28,100	0.95	0.57	63	47.0
	(b) With damage to the liver.....	24,600	225	0.58	0.45	61	55.0
		E : Vitamin A		E : Carotene		Vitamin A E : Carotene $\times 10^{-3}$	
I and II.....		3.9		2.4		1.3	
I and III.....		7.2		5.3		4.4	
I and IV.....		4.1		3.8		1.2	
I and V(a).....		3.1		2.7		0.99	
I and V(b).....		6.0		4.6		0.08	

by infection. The carotene content of the liver of patients in this group was within normal limits. The carotene contents of the liver of the 3 patients with diabetes were 0.85, 1.40 and 1.70 mg. per hundred grams of liver. The vitamin A contents of the livers of the patients with diabetes were 58,000, 59,000 and 75,000 U. S. P. units per hundred grams of liver.

GROUP VII: *Malignant Conditions* (7 patients; table 4).—In this group there were 4 cases of carcinoma, in 2 of which there were metastases to the liver. There was 1 case each of lymphosarcoma, leukemia and hypernephroma. In 5 cases the nutritional state was poor. In 6 cases the patient was over 55 years of age.

The vitamin A content of the liver was low in 3 of the 7 patients, with a corresponding reduction in the carotene content of the liver.

Curiously enough, the patient with lymphosarcoma, although emaciated, had a high value for both vitamin A and carotene. This patient had metastatic nodules in the liver, and the question arises whether these nodules may have stored vitamin A.

GROUP VIII: *Cardiovascular Diseases* (16 patients; table 4).—This group consists of patients with hypertensive, arteriosclerotic and syphilitic heart disease. Four of these patients had coronary thrombosis. In only 7 of the patients was the liver normal on pathologic examination. In 3 patients there was chronic passive congestion; in 3 patients the state of the liver was not reported, and in the remaining patients there was either cirrhosis or fatty infiltration. Ten of the patients had vitamin A values for the liver within normal limits. The average for the group was 58,300 U. S. P. units per hundred grams of liver. The value for carotene ranged from 0.76 to 3.30 mg. per hundred grams of liver. The average for the group was normal.

COMMENT

A summary of the findings for the various groups is given in table 4, which permits a comparison of the average results for each group. If one accepts the fact that the normal liver will contain at least 40,000 U. S. P. units of vitamin A per hundred grams of liver, the striking reductions in the concentration of this substance are found to occur in the patients with cirrhosis of the liver and in the patients with acute infections, who in addition showed some pathologic change in the liver, such as cirrhosis or fatty infiltration. Although the average vitamin A content of the liver of the patients with alcoholism and of those with chronic infectious disease does not show the same consistent reduction, in each of these groups there were many cases in which the vitamin A content of the liver was significantly lowered. It is particularly interesting to note that of the 16 patients with alcoholism who had a lowered vitamin A content of the liver, the condition in 11 was complicated by either cirrhosis of the liver or by infection.

The finding of a low concentration of vitamin A in these patients with cirrhosis of the liver is consistent with the observation of Patek and Haig⁹ that patients with such a condition had impairment of dark adaptation.

The carotene content of the liver was significantly low in the same groups of patients, for example, those with cirrhosis and acute infections in which there was an associated pathologic change in the liver. The same general fact holds true for the averages for carotene as for the

9. Patek, A. J., Jr., and Haig, G.: Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, *J. Clin. Investigation* **18**:609, 1939.

averages for vitamin A, and the carotene values were low for those patients with alcoholism for whom the vitamin A content of the liver was low.

The objective analysis of the results of the vitamin A and the carotene determinations are shown in table 5. In calculating the standard deviations the average value for vitamin A for the normal group was taken as 76,600 instead of 121,000 U. S. P. units per hundred grams of liver. The former is the average value obtained when the figures for the 2 subjects (cases 76 and 81) with extremely high concentrations of vitamin A are omitted. The values for carotene were treated in the same way. The standard deviations are fairly large. This is to be expected, as the ages of these persons varied from the first decade to the eighth, the diets were an unknown factor and probably subject to considerable variation and the nutritional states of the subjects differed. However, when the average vitamin A content of the liver obtained in this group of normal persons is compared with the average content for the various groups of diseased patients, we find that the E value for vitamin A shows that the differences are significant in all groups. The same is true for carotene.

If one takes 40,000 U. S. P. units per hundred grams of liver as the normal vitamin A content of the liver, which would be indicated by Crimm and Short's results, significant differences as expressed by the E value occur only in the groups of patients with cirrhosis of the liver and with acute infections associated with damage to the liver. The ratio of vitamin A to carotene was significantly reduced only in the group of patients with cirrhosis of the liver. The importance of this ratio in the various groups is minimized, owing to the wide variation in each group. As mentioned before, we have previously suggested¹⁰ that the ability of the liver to convert carotene to vitamin A may be interfered with under certain circumstances. Obviously, cirrhosis of the liver accompanied by severe damage to the liver might provide such a condition.

The fact that in the cases of acute infection in which there was also some pathologic change in the liver there was a significant reduction of vitamin A stresses the role of the liver as a storehouse of vitamin A. Previous reports have suggested that infection depletes the stores of vitamin A in the liver. The fact that in cases of acute infection associated with a pathologic condition of the liver the vitamin A and carotene

10. Ralli, E. P.; Pariente, A. C.; Brandaleone, H., and Davidson, E.: Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus, *J. A. M. A.* **106**:1975 (June 6) 1936. Ralli, E. P.; Brandaleone, H., and Mandelbaum, T.: Studies on the Effect of the Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus, *J. Lab. & Clin. Med.* **20**:1266, 1935.

contents of the liver were almost 50 per cent lower than in the cases of acute infection uncomplicated by any pathologic condition of the liver suggests that the pathologic condition of the liver is a more significant factor in maintaining the normal vitamin A stores of the liver than is infection per se. Probably the condition of the liver and the vitamin A content of the diet are the two most important factors in determining the concentration of the vitamin in the liver.

SUMMARY

The vitamin A and carotene contents of the livers of 116 subjects are reported. Twenty-five of the patients were normal persons as far as could be ascertained and served as a basis of comparison for the other groups.

In the patients with cirrhosis of the liver and in those with acute infection and an associated pathologic condition of the liver there was a striking decrease in the vitamin A and the carotene content of the liver. The ratio of vitamin A to carotene was significantly altered only in the group of patients with cirrhosis of the liver.

It is suggested that the factors that determine the vitamin A content of the liver are the dietary intake of vitamin A and the pathologic state of the liver. At present cirrhosis of the liver seems to be the most important pathologic disturbance.

HEMORRHAGIC DIATHESES

AN ANALYSIS OF THREE HUNDRED AND FIFTY-FIVE AUTOPSY REPORTS

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All too frequently the word *purpura* is used as a diagnosis. This is obviously unsound, since the word has been employed to describe anything from a minute petechia to gross capillary hemorrhage. Since *purpura* is derived from the Greek word *πορφυρα*, meaning "purple," its use should be limited purely to description.

The term hemorrhagic diathesis is more accurate than the older term *purpura*. It may be correctly applied to any extravasation of blood through the endothelial wall of the capillaries, regardless of amount. Hence, it includes not only the external, visible evidences of capillary damage, such as bleeding into the skin, the oral mucosa, the nasal mucosa or the conjunctiva, but also the hidden bleeding from the mucosa or the serosa of the internal organs.

Tidy¹ coined the term "angio-staxis" to include the "primary" purpuras and the various manifestations of the hemorrhagic states. However, there is no need for the introduction of a new term into an already confused nomenclature. Hemorrhagic diathesis, qualified by the phrase "on the basis of," is an accurate diagnostic and descriptive term.

CLASSIFICATION OF THE HEMORRHAGIC STATES

There are three factors that may be the precipitating cause of a hemorrhagic diathesis. These are:

1. Damage to or weakness of the capillary endothelium.
2. A deficiency of the clot-forming elements.
3. Faulty clot retraction, due to a decreased number of platelets.

These factors are used as the basis of the main divisions in the various classifications of the hemorrhagic states. Similar schemes are

From the Department of Medicine, Cook County Hospital.

1. Tidy, H. L.: Hemorrhagic Diathesis: Angio-Staxis, *Lancet* **2**:365, 1926.

followed by Downey,² Whitby and Britton,³ Kracke and Garver,⁴ Osler,⁵ Mettier⁶ and Peck, Rosenthal and Erf.⁷ The essential difference in the various classifications lies only in the subgroups and smaller divisions of the three main etiologic types of abnormal bleeding.

The following classification which we have used in the analysis of our material differs only in its subdivisions from those referred to.

I. Hemorrhagic diatheses due to platelet deficiencies

- A. "Essential" thrombopenia
(idiopathic thrombopenic purpura)
- B. Allergic thrombopenia
- C. Symptomatic thrombopenia—caused by bone marrow deficits
 - 1. Blood dyscrasias
 - 2. Multiple metastases to bone marrow
 - 3. Gaucher's disease and other lipoid dystrophies

II. Hemorrhagic diatheses due to changes in the capillary walls

- A. Anaphylactoid states
- B. Infectious states
 - 1. Acute infections
 - 2. Chronic infections
- C. Nephritic "toxins"
- D. Drug intoxications
- E. Vitamin deficiencies (C and P)

III. Hemorrhagic states due to changes in the clotting elements of the blood

- A. Diseases of the liver
 - 1. Atrophy of the liver
 - 2. Cirrhosis of the liver
 - 3. Obstructive jaundice
- B. Vitamin K deficiency
- C. Hemorrhagic disease of the newborn
- D. Icterus neonatorum
- E. Hemophilia

2. Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 1.

3. Whitby, L. E. H., and Britton, C. J. C.: *Disorders of the Blood*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1937.

4. Kracke, R. R., and Garver, H. E.: *Diseases of the Blood and Atlas of Hematology*, Philadelphia, J. B. Lippincott Company, 1937.

5. Osler, W.: *Modern Medicine: Its Theory and Practice*, Philadelphia, Lea & Febiger, 1908, vol. 4.

6. Mettier, S. R.: *Classification and Treatment of the Hemorrhagic States*, J. A. M. A. **108**:83 (Jan. 9) 1937.

7. Peck, S. M.; Rosenthal, N., and Erf, L.: *Purpura: Classification and Treatment*, Arch. Dermat. & Syph. **35**:831 (May) 1937.

ANALYSIS OF CASES

The material used in this analysis was obtained from the autopsy reports of the Cook County Hospital from 1929 to 1937. During this period 10,355 autopsies were performed. Of this number 355 revealed evidences of hemorrhagic diatheses, an incidence of 3.4 per cent. On the basis of the anatomic diagnosis, all cases in which there were hemorrhagic manifestations were investigated, and a correlation was attempted between the type of diathesis and its probable cause.

The classification we have given in the preceding section is one adapted to clinical use. The summary of the pathologic reports will include some, but not all, of the clinical types.

I. Hemorrhagic diatheses due to platelet deficiencies, 21.9%	
A. Essential thrombopenia	6
B. Symptomatic thrombopenias	
1. Blood dyscrasias	
(a) Leukemias	39
(b) Aplastic anemia	12
(c) Hodgkin's disease	3
(d) Pernicious anemia	3
(e) Sickle cell anemia	2
(f) Hemolytic anemia	1
2. Multiple metastases to bone marrow	12
II. Hemorrhagic diatheses due to changes in the capillary walls	
A. Infectious states, 49.3%	
1. Acute infections	
(a) Septicemia	14
(b) Otitis media.....	3
(c) Meningitis	30
(d) Pneumonia	11
(e) Typhoid fever.....	2
(f) Endocarditis	96
(g) Gangrenous pharyngitis	1
(h) Pyonephrosis.....	4
2. Chronic infections	
(a) Tuberculosis	12
(b) Abscess of the lung	2
B. Toxins of nephritic origin, 16.3%	
1. Benign nephrosclerosis	20
(associated with eccentric hypertrophy of the heart)	
2. Malignant nephrosclerosis	16
3. Subacute and chronic	16
glomerular nephritis	
4. Acute glomerular nephritis	5
5. Mercury bichloride poisoning	1

III. Hemorrhagic states due to changes in the clotting elements of the blood

A. Diseases of the liver, 7.3%

- | | |
|---|---|
| 1. Atrophy of the liver | 4 |
| 2. Cirrhosis of the liver | 9 |
| 3. Obstructive jaundice | |
| (a) Common duct stone..... | 2 |
| (b) Adenocarcinoma of the biliary tract | 5 |
| 4. Toxic hepatitis | 4 |
| 5. Carcinoma with extensive metastases to the liver | 2 |

B. Hemorrhagic disease of the newborn, 1.4%..... 5

Icterus neonatorum, 1.1%..... 4

IV. Unclassified hemorrhagic states, 2.5%

- | | |
|--|---|
| A. Congenital syphilis | 3 |
| B. Atelectasis | 2 |
| C. Eclampsia | 1 |
| D. Coronary thrombosis | 2 |
| E. Waterhaus-Friedrichsen syndrome | 1 |

It now becomes evident that in the differential diagnosis of bleeding states, essential thrombopenic purpura plays a minor role, accounting for only 1.7 per cent of all the cases. The blood dyscrasias themselves account for less than one fifth of the material. From our analysis, the most important cause of the hemorrhagic diatheses appears to be the infectious states, since they include up to 50 per cent of the entire series of cases. Among the infectious conditions, bacterial endocarditis is the greatest offender, causing 27 per cent of all the hemorrhagic diatheses. Next in importance is meningitis, which is encountered in 8.5 per cent of the material.

Ranking almost equally in importance with the blood dyscrasias as a cause of abnormal bleeding states are the hemorrhagic diatheses produced by toxins of nephritic origin. These include the nephroscleroses, both benign and malignant, and the glomerular nephritides of the acute, subacute and chronic varieties.

Accounting for 9.8 per cent of the total number of cases are those instances of hemorrhagic states associated with jaundice. The 1 case of hemolytic anemia has been included with the blood dyscrasias. In all cases the condition was dependent on some type of damage to the liver which, in addition to causing icterus, produced changes in the clotting elements of the blood plasma, with a resultant increase in the bleeding or clotting time.

Briefly summarized, the relative frequency of the factors in the production of the hemorrhagic states may be listed as follows:

- | | |
|--------------------------------------|-------|
| 1. Infectious diseases | 49.3% |
| 2. Platelet deficiencies | 21.9% |
| 3. Pathologic renal conditions | 16.3% |
| 4. Hepatic disorders | 9.8% |

CORRELATION OF PATHOLOGIC MANIFESTATIONS WITH
ETIOLOGIC FACTORS

The mode of production of the hemorrhagic diatheses by the pathologic phenomena just listed is of great interest. We shall attempt to explain each anatomic cause of bleeding by references to similar cases reported and by an evaluation of the physiologic processes involved.

The hemorrhagic diatheses due to platelet deficiencies include the essential thrombopenia (idiopathic thrombopenic purpura) and the symptomatic thrombopenias. In all these conditions there is an actual reduction in the number of platelets in the circulating blood. The reduction in the number of platelets in essential thrombopenia may be due to an actual decrease in the number of megakaryocytes in the bone marrow, to a defect in the maturation of the megakaryocytes with a decreased extrusion of platelets⁸ or to actual destruction of the platelets in the spleen.⁹ The destruction of platelets in the spleen is the most plausible theory, since splenectomy is followed by a rapid increase in the number of platelets in the circulating blood. However, recent experimental studies have shown that there is a substance in the splenic tissue which is injurious to the megakaryocyte.¹⁰ From this it may be assumed that platelets are restored after splenectomy by the removal of the platelet-inhibiting factor secreted by the spleen or by the removal of a substance which inhibits the maturation of the megakaryocytes.

The reduction in the number of platelets found in the symptomatic thrombopenias is due to a quantitative decrease in the number of megakaryocytes in the bone marrow or, again, to an inhibition of the substance effecting maturation of the megakaryocytes. Either of these factors would make for a decrease in the number of platelets in the circulating blood. The group of cases of hemorrhagic states due to changes in the capillary wall, next to be discussed, makes up the largest in our series, 233 of a total of 355, and the condition is caused by any factor which may tend to damage the wall of the vessels.

We have listed no cases in the anaphylactoid or allergic groups, despite the many reports in the literature concerning such conditions.¹¹

* 8. Frank, E.: *Haemorrhagische Diathesen*, in Klemperer, G., and Klemperer, F.: *Neue deutsche Klinik*, Berlin, Urban & Schwarzenberg, 1930, vol. 4, p. 395.

9. Kaznelson, P.: *Erfahrungen über die Indikationen der Splenectomie und über deren Wirkungsmechanismus*, *Wien. Arch. f. inn. Med.* **7**:87, 1923.

10. Torrioli, M., and Puddu, V.: *Recent Studies on the Pathogenesis of Werlhof's Disease*, *J. A. M. A.* **111**:1455 (Oct. 15) 1938. Troland, C. E., and Lee, F. C.: *Thrombocytopenic Substance in Extract from Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces Number of Blood Platelets*, *ibid.* **111**:221 (July 16) 1938.

11. Fox, M. J., and Enzer, N.: *A Consideration of the Phenomenon of Purpura Following Scarlet Fever*, *Am. J. M. Sc.* **196**:3, 1938. Ellis, R. W. B.: *Allergic*

In most of the cases in which the diathesis was reported as due to allergic reactions of the capillary wall the forerunner was an infectious or a toxic process which might well have been the etiologic agent in the injury of the capillary wall.

The infectious diseases, both acute and chronic, are the greatest offenders in the production of a weakened capillary wall and the resultant escape of the cellular elements of the blood stream. This damage to the capillary wall may be brought about in several ways. Bacterial emboli may lodge in the small bore capillaries. This results in a direct necrotic action on the vessel wall, as in bacterial endocarditis, generalized septicemias and typhoid fever. Damage to the wall may also be caused by weakening and breaking of the endothelial lining of the capillary due to the action of the toxins produced by the bacteria, as in pneumonia and meningitis.

Purpuric lesions have been noted in association with tuberculosis and are regarded as a poor prognostic sign in this disease.¹² Fishberg¹³ expressed the belief that the presence of purpura in tuberculosis is merely a coincidence. However, both Cruice^{12a} and Houcke and Boury^{12b} suggested that the pathogenic factor in the purpuric eruption associated with tuberculosis is the absorption of toxins from rapidly breaking down tuberculous foci. Since both conditions are met with in the terminal stages of tuberculosis, the presence of a hemorrhagic diathesis in the course of a tuberculous infection may be viewed as evidence of increased activity of the tubercle bacillus.

The presence of a hemorrhagic diathesis of nephritic origin must always be kept in mind in the differential diagnosis of the hemorrhagic states. Fisher¹⁴ was the first to suggest that toxins might be present in the blood of persons with nephritic disease. These toxins, by means of a destructive action on the capillary endothelium, might be capable of causing hemorrhagic extravasations. Riesman¹⁵ held that the bleeding was due either to the hypertension which is usually present or to toxemia. He drew attention to the serious prognostic significance of a

Purpura, *Proc. Roy. Soc. Med.* **31**:768, 1938. Stoesser, A. V., and Lockwood, W. W.: Varicella Complicated with Acute Thrombocytopenic Purpura and Gangrene, *J. Pediat.* **12**:641, 1938.

12. (a) Cruice, J. M.: The Incidence of Purpura in the Course of Chronic Pulmonary Tuberculosis, *Am. J. M. Sc.* **144**:875, 1912. (b) Houcke, E., and Boury, M.: Purpura et tuberculose pulmonaire, *Sang* **12**:44, 1938.

13. Fishberg, M.: *Pulmonary Tuberculosis*, Philadelphia, Lea & Febiger, 1932.

14. Fisher, T.: Haematemesis Associated with Small White Kidneys, *Bristol Med.-Chir. J.* **22**:243, 1904.

15. Riesman, D.: Hemorrhages in the Course of Bright's Disease, with Special Reference to the Occurrence of a Hemorrhagic Diathesis of Nephritic Origin, *Am. J. M. Sc.* **134**:709, 1907.

hemorrhagic diathesis in nephritis. The most plausible cause of a hemorrhagic state in nephritis is the retention of nitrogenous products and the occurrence of uremia,¹⁶ which exert a damaging effect on the capillaries of the entire body.

Of interest in the causation of a hemorrhagic diathesis by toxins of nephritic origin is an incidental observation by Drury.¹⁷ In the course of experiments on the production of renal insufficiency in rabbits, he noted hemorrhages in the intestinal wall and bleeding into the lumen of the intestinal tract at autopsy.

The purpuric manifestations occurring in acute nephritis are most likely due to toxemia of streptococcic origin and as such are distinct from those caused by the chronic forms of nephritis.

Several of our cases in which there was only a slight nitrogen retention (up to 50 mg. of nonprotein nitrogen per hundred cubic centimeters of blood) were included with those of the hemorrhagic diatheses due to toxins of nephritic origin. The patients in all of these cases had an elevation of blood pressure of over 150 mm. of mercury systolic. The occurrence of a bleeding tendency in those patients may be explained by the findings of Levrat and Ballivet.¹⁸ They found that of 7 persons without hypertensive disease, over 60 years of age, only 1 gave a positive reaction to a tourniquet test, while of 33 persons with proved hypertension, 4 of whom were under 50 years of age, all but 2 showed a positive reaction to a tourniquet test. They postulated that the factor involved in the production of the purpuric eruptions was mechanical, due to an increased arterial pressure transmitted to the capillaries, or was based on an increased capillary fragility.

The 1 case of mercury bichloride poisoning which we included in our series may be explained by the marked nitrogen retention produced by the action of mercury on the kidney.

Before leaving the hemorrhagic states which are due to changes in the capillary wall, it may be fitting to mention the effect of vitamin C. It has long been known that the presence of vitamin C in the diet is of importance in the prevention of scurvy. The scorbutic states are manifested by bleeding from the gums, into the skin and subperiosteally. That vitamin C is necessary in the maintenance of the integrity of the capillary wall has been shown in many ways. Roberts and his

16. Davidson, L. S. P.; Davenport, C., and Rabagliati, D. S.: Discussion on Purpuric Conditions in Man and Animals, *Proc. Roy. Soc. Med.* **30**:715, 1937. Fishberg, A. M.: *Hypertension and Nephritis*, Philadelphia, Lea & Febiger, 1939, pp. 182 and 672.

17. Drury, D. R.: *Renal Insufficiency and Hypertension*, *J. Exper. Med.* **68**: 693, 1938.

18. Levrat, M., and Ballivet, J.: *Le purpura provoqué chez les hypertendus*, *Lyon méd.* **163**:243, 1939.

associates¹⁹ estimated the capillary fragility in children with the Dall-dorf resistometer. They found a distinct seasonal change in the capillary fragility, which became greatest at the time when vitamin C was lowest in the diet. Liebmann and his co-workers²⁰ attempted to correlate the capillary fragility with the vitamin C content of the blood. They found a 70 to 75 per cent agreement between the level of vitamin C in the blood and the result of the Rumpel-Leeds tourniquet test.

More recently, Szent-Györgyi and his associates²¹ have brought forth the claim that vitamin P (pure citrin— $C_{25}H_{36-38}O_{17}$) is concerned with the maintenance of normal permeability of the capillaries. Jersild²² reported the cure of a patient with Schönlein-Henoch purpura by the use of citrin itself.

The hemorrhagic conditions due to changes in the clotting elements of the blood are all dependent on underlying pathologic changes in the liver and an increase in the prothrombin time of the blood. The absence of adequate amounts of the antihemorrhagic factor in the diet and the faulty absorption of vitamin K through the intestinal mucosa are causes of abnormal bleeding which have only recently been emphasized.²³

We have included 35 cases of hemorrhagic diatheses associated with jaundice. Of these, 7 were cases of obstructive jaundice in which there was a lack of absorption of vitamin K due to the absence of bile from the intestine. With this absence there occurs a lowering of the level of prothrombin in the blood.²⁴ In the presence of severe hepatic disease, such as atrophy, cirrhosis, hepatitis and extensive carcinomatous

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deposits, there is a derangement in the metabolism of prothrombin. This in turn causes a hemorrhagic tendency, due to the inability of the blood elements to form thrombin.

The same factors also operate in hemorrhagic disease of the newborn, as shown by Waddell and Guerry,²⁵ and are the cause of the bleeding tendency in jaundice of the newborn.

There remain 9 cases which we have been unable to classify. The 3 cases of congenital syphilis may possibly be explained by a weakening of the capillary wall caused by the syphilitic infection. The 2 cases of coronary thrombosis which were accompanied by hemorrhagic lesions may be explained by the concomitant hypertension and consequent weakening of the capillary wall, as was earlier hypothesized.

The 2 cases of atelectasis which we encountered present a more difficult problem. Perhaps the hemorrhagic state may here be due to the concomitant anoxemia, which is characterized by minute hemorrhages into the submucosa and the subendothelial areas. Again, it may be a manifestation of the hypoprothrombinemia from which some newborn and older infants suffer.

The purpuric manifestations seen in the case of eclampsia may be due to the hepatic damage produced by the toxemia.

In the case of the Waterhaus-Friedrichsen syndrome the classic changes of hemorrhage into the adrenal glands and of purpuric spots in the skin were presented. Whether this was due to an underlying sepsis or to a congenital weakness of the capillary bed cannot be ascertained at present.

SUMMARY

1. The scope of the term "hemorrhagic diathesis" is defined.
2. The hemorrhagic diatheses are classified on the basis of physiologic alterations in the blood and in the vessel walls.
3. The pathologic manifestations of the hemorrhagic diatheses are correlated with the etiologic factors.

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TREATMENT OF LOBAR PNEUMONIA WITH RABBIT ANTIPNEUMOCOCCUS SERUM

EFFICACY OF THE PROJECTED DOSE METHOD OF TREATING PNEUMONIA
WITH HOMOLOGOUS REFINED AND UNCONCENTRATED
RABBIT ANTIPNEUMOCOCCUS SERUM

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During the past year pneumococcic pneumonia was treated almost exclusively with chemotherapeutic substances. Pneumonia during this period was relatively mild, and bacteremia was infrequent. A decreased mortality rate for pneumonia, which could not be attributed entirely to specific measures, was noted. We feel, therefore, that a study of the results obtained with a specific therapeutic agent during a previous period in which pneumonia was known to be more severe and in which there was a higher incidence of bacteremia should be presented at this time.

Rabbit antipneumococcus serum was first used by Horsfall, Goodner and MacLeod¹ in 1936. In 1937, these authors and an associate² described 22 cases in which this serum was used. In 1938, the first three authors reported the results obtained with homologous serum in 67 cases of types I, II, III, V, VI, VII, VIII, XIV and XVIII pneumococcus pneumonia in which the mortality rate was 3.7 per cent when 13 cases of type III pneumococcus pneumonia were excluded.³

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In 1938, we reported 69 cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia treated with homologous refined and unconcentrated rabbit antipneumococcus serum.⁴ In this series the mortality rate was 7.4 per cent. In 1939, we reported a series of 125 cases of types V, VII and VIII pneumococcus pneumonia in which only 2.4 per cent of the patients died.⁵

Wood,⁶ in 1939, published a report of 50 cases of types I, II, III, IV, V, VI, VII, VIII and XIV pneumococcus pneumonia in which treatment was with rabbit antipneumococcus serum and in which the mortality rate when 8 cases of type III pneumococcus pneumonia were excluded was 14.3 per cent.

Volini and Levitt,⁷ in 1939, studied twenty-one types of pneumonia in 153 cases in which rabbit antipneumococcus serum was used and in which the corrected mortality rate was 7.2 per cent.

It is the purpose of our present paper to summarize the studies made in 320 cases of types I, II, V, VII, VIII and XIV pneumococcus lobar pneumonia treated with homologous refined and unconcentrated rabbit antipneumococcus serum.

METHODS AND MATERIAL

Antipneumococcus Serums.—The rabbit antipneumococcus serum used in treatment in these cases was unconcentrated but refined, having been prepared according to the methods of Goodner, Horsfall and Dubos.⁸

Cases.—From December 1937 to April 1939 inclusive, the cases of 320 patients with pneumonia were studied in the pneumonia service of the Long Island College Hospital and the medical services of the Kings County Hospital. Many of the patients had received no medical treatment prior to their admission to the hospital. The study was based on an unselected consecutive series of cases. The cases of 8 patients were excluded from the analysis of results for the following reasons: One patient had a type V pneumococcus acute bacterial endocarditis at the time of admission to the hospital. Another patient had a *Streptococcus viridans* subacute bacterial endocarditis and a terminal type VII pneumococcus pneumonia.

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In both cases, at autopsy, the endocarditis was found to be the primary cause of death. Another patient had a cerebral hemorrhage prior to admission and died within five hours after serum treatment was started. The remaining patients, moribund on admission, died between three and ten hours after serum therapy was begun. The cases of patients who lived more than twelve hours after they received the first dose of serum were included in the analysis.

Typing.—The sputum was cultured, and the typing of pneumococci, which was done according to the Neufeld method, was confirmed by mouse inoculation. When satisfactory specimens of sputum could not be obtained, culture of material from the lung was made.

Blood cultures were made prior to administration of serum and usually at intervals of twenty-four hours during the febrile period.

Examinations.—When the patient was admitted to the hospital, the history was taken and a physical examination and studies of the blood were made. The diagnosis was confirmed roentgenologically.

The Francis test was made in a number of cases prior to and during serum therapy, and at times it was used to determine the necessity of additional serum. The clinical appearance of the patient, however, generally determined the course of therapy.

Sensitivity Tests.—Intravenous: One tenth of a cubic centimeter of rabbit antipneumococcus serum diluted to 5 cc. with physiologic solution of sodium chloride was injected into a vein. The blood pressure and the heart rate were determined just prior to, and five minutes after, the injection of this test dose of serum. The patient was considered sensitive to rabbit serum if there was a fall in blood pressure of 20 mm. of mercury or an increase in the heart rate of twenty beats per minute.

Conjunctival: One tenth of a cubic centimeter of a 1:10 dilution of rabbit serum was dropped into a conjunctival sac. Sensitivity of the patient to the serum was manifested by itching, lacrimation, congestion, and swelling of the conjunctiva.

Dosage of Rabbit Antipneumococcus Serum.—In August 1938, we reported the cases of 69 patients, to each of whom a predetermined or projected dose of rabbit antipneumococcus serum was given; of these, 40 were successfully treated with a single dose.⁴

In September 1939,⁵ we reported the cases of 125 patients, and of these, 102 were successfully treated with a single projected dose.

To all the patients whose cases are reported in this present paper, a projected dose of rabbit serum was administered. This is the quantity of serum, measured in Felton units, that we have found adequate to produce a crisis in the average case of pneumococcic lobar pneumonia.

Determination of Dose: When a patient was less than 40 years of age, had been ill less than sixty hours, had involvement of no more than one lobe and had neither complications nor bacteremia, 160,000 units was given in cases of types I, V and VIII pneumococcus pneumonia, while in cases of types II, VII and XIV pneumococcus pneumonia 200,000 units was given. However, in January, February, March and April, because of the high incidence of infections of the respiratory tract, diminished resistance on the part of the patients and the increased virulence of the pneumococci, 200,000 units was administered in cases of types I, V and VIII pneumococcus pneumonia and 260,000 units in cases of types II, VII and XIV pneumococcus pneumonia.

When a patient was over 40 years of age, had been ill more than sixty hours, had involvement of more than one lobe and had complications or bacteremia, 200,000 units was given in cases of types I, V and VIII pneumococcus pneumonia, while in cases of types II, VII and XIV pneumococcus pneumonia 300,000 units was given. An additional 60,000 units in cases of types I, V and VIII pneumococcus pneumonia and 100,000 units in cases of types II, VII and XIV pneumococcus pneumonia was given during January, February, March and April.

Leukopenia, particularly in cases of type VIII pneumococcus pneumonia, indicated to us the probability of bacteremia. When leukopenia was noted, the projected dose considered necessary in a case of bacteremia was given.

Subsequent doses of serum, when necessary, were usually administered at intervals of twenty-four hours. The quantity was determined by the clinical condition of the patient, the presence or absence of bacteremia, the response to the previous dose and, at times, the results of the Francis test. We used the pulse rate and the respiratory rate as clinical guides for determining the necessity of further therapy. When either remained elevated, more serum was given.

Administration of Rabbit Antipneumococcus Serum.—When a patient was found not to be sensitive to rabbit antipneumococcus serum, the projected dose of serum was administered intravenously. From 10 to 15 grains (0.6 to 1 Gm.) of acetylsalicylic acid was given orally just prior to the administration of the serum and before each subsequent dose.

A syringe containing a solution of epinephrine hydrochloride (1:1,000) was always available at the bedside. Heat was never applied to the serum, which preferably was warmed in the hands or was allowed to stand until it reached room temperature.

The cuff of the sphygmomanometer was placed around the arm other than the one into which the serum was to be given. The serum was administered with an intravenous drip infusion set. A physiologic solution of sodium chloride was allowed to flow into the vein and after the rate was regulated, the administration of the serum was begun. When the level of the serum had reached the outlet of the infusion flask, an additional 25 to 50 cc. of physiologic solution of sodium chloride was poured into the flask to insure complete utilization of the serum in the tubing.

The pulse rate was observed during the administration of serum. When there was a significant increase in the rate or when the patient presented reactions which were considered anaphylactoid or anaphylactic, the flow of serum was temporarily discontinued and a determination of blood pressure made.

When there was no decrease in the blood pressure, the administration of serum was allowed to continue. However, when a decrease in blood pressure of 20 mm. of mercury or more was noted, 1 or 2 minims (0.06 to 0.12 cc.) of a solution of epinephrine hydrochloride (1:1,000) was injected into a vein. When the blood pressure had returned to the previous level, the serum was then permitted to flow very slowly.

RESULTS

Pneumonia Due to Pneumococcus Type I.—One hundred and twenty-six patients with type I pneumococcus pneumonia were treated with type I refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). In 53 cases there was consolidation of two or more lobes, and in 13 bilateral consolidation was found. Thirty-four patients had bacteremia. The pneumonia had been present for an average of

ninety-five hours, with extremes of fifteen hours and two hundred and forty hours, before rabbit serum was administered. Ninety patients had pneumonia seventy-two hours or more before treatment (chart 2). The average amount of serum given was 316,000 units. The temperature fell to normal in an average of fourteen hours, with extremes of two hours and ninety-two hours.

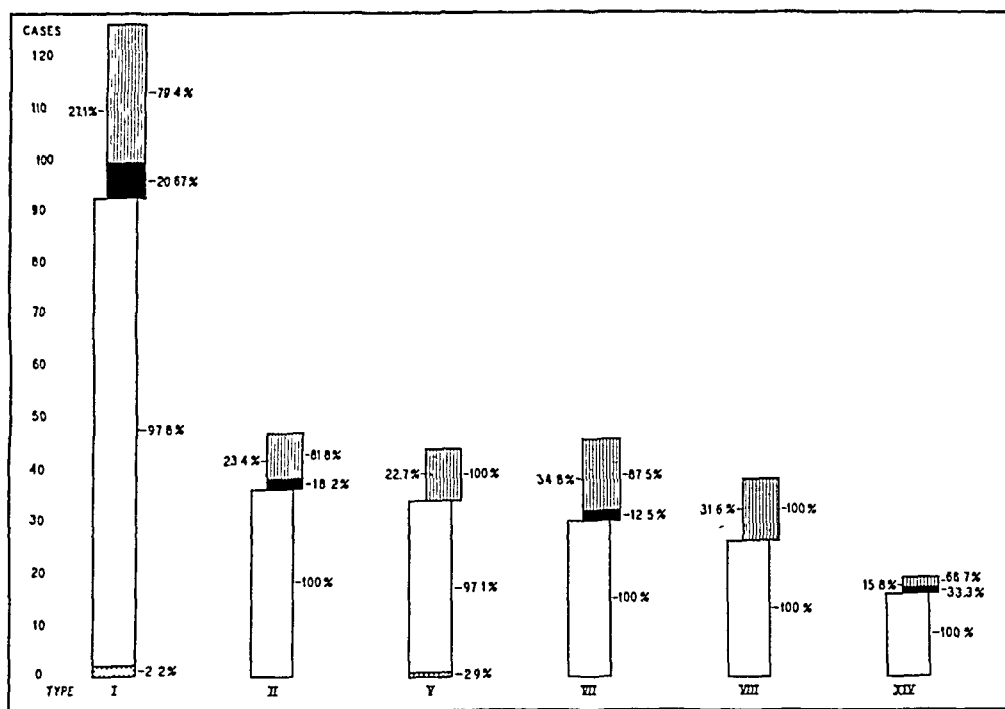


Chart 1.—Incidence of bacteremia (percentage at left of column) and survival and death (percentage at right of column) in 320 cases of pneumococcal pneumonia treated with homologous rabbit antipneumococcus serum. The markings of each column signify the following conditions: vertical lines, bacteremia present, outcome favorable; solid black, bacteremia present, outcome fatal; solid white, bacteremia absent, outcome favorable, and cross-hatching, bacteremia absent, outcome fatal.

TABLE 1.—*Pneumococcal Pneumonia Treated with Homologous Rabbit Antipneumococcus Serum*

Type	Number of Cases	Bacteremia	Interval Between Onset and First Dose of Serum, Average (Hr.)	Total Dose of Serum, Average (Units)	Number of Successful Single Doses	Interval Between First Dose of Serum and Crisis, Average (Hr.)	Serum Sickness	Mortality, Percentage
I.....	126	34	95	316,000	100	11	41	7.1
II.....	47	11	94	350,000	35	20	23	4.3
V.....	44	10	89	312,000	35	14	9	2.3
VII.....	46	16	83	340,000	36	15	9	4.4
VIII.....	38	12	80	300,000	34	12	9	0.0
XIV.....	19	3	111	333,000	12	36	8	5.3
Total.....	320	86			252			
Average.....			92 hr.			18.5 hr.		
Percentage.....		27			79			4.7

One hundred patients, of whom 15 had bacteremia, were successfully treated with one dose of serum, and in these crisis occurred in an average of twelve hours. The average single successful dose was 257,000 units.

Serum sickness developed in 41 patients.

One hundred and seventeen patients recovered, and 9 died. The mortality rate for type I pneumococcus pneumonia was 7.1 per cent.

Pneumonia Due to Pneumococcus Type II.—Forty-seven patients with type II pneumococcus pneumonia were treated with type II refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Thirteen patients had consolidation of two or more lobes, and, of these, 5 had bilateral processes. Eleven patients had bacteremia. The onset of the pneumonia had occurred on an average of ninety-four hours, with extremes of sixteen hours and two hundred and sixty hours, before rabbit serum was administered. In 31 cases the pneumonia had been present seventy-two hours or more before treatment was begun (chart

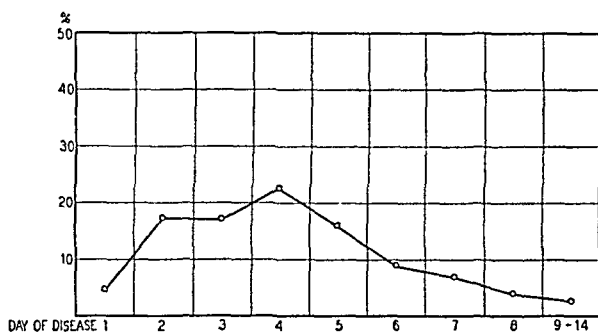


Chart 2.—Day of disease on which therapy with homologous rabbit antipneumococcus serum was begun in 320 cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia.

2). The average amount of serum given was 350,000 units. The temperature became normal in an average of twenty hours, with extremes of four hours and one hundred and twenty hours.

Thirty-five patients, of whom 8 had bacteremia, were successfully treated with one dose of serum. In these patients crisis occurred in an average of ten hours. The average single successful dose was 260,000 units.

Serum sickness developed in 23 cases.

Forty-five patients recovered, and 2 died. The mortality rate for type II pneumococcus pneumonia was 4.3 per cent.

Pneumonia Due to Pneumococcus Type V.—Forty-four patients with type V pneumococcus pneumonia were treated with type V refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Thirteen patients had consolidation of two or more lobes, and 8 of these

had bilateral involvement. Bacteremia was found in 10 cases. The pneumonia had been present for an average of eighty-nine hours, with extremes of twenty-six hours and one hundred and ninety-two hours, before rabbit serum was administered. Twenty-nine patients were treated after the pneumonia had been present seventy-two hours or more (chart 2). The average amount of serum given was 312,000 units. The temperature fell to normal in an average of fourteen hours, with extremes of three hours and forty-eight hours.

Thirty-five patients, of whom 7 had bacteremia, were successfully treated with one dose of serum, and in them crisis occurred in an average of nine hours. The average single successful dose was 231,000 units.

Serum sickness developed in 9 patients.

Forty-three patients recovered, and 1 died. The mortality rate for type V pneumococcus pneumonia was 2.3 per cent.

Pneumonia Due to Pneumococcus Type VII.—Forty-six patients with type VII pneumococcus pneumonia were treated with type VII refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). In 19 cases there was consolidation of two or more lobes; while in 7 bilateral consolidation was found. Sixteen patients had bacteremia. The pneumonia had been present for an average of eighty-three hours, with extremes of twenty hours and one hundred and ninety-two hours, before rabbit serum was administered. Thirty patients had pneumonia seventy-two hours or more before treatment (chart 2). The average amount of rabbit serum given was 340,000 units. The temperature became normal in an average of fifteen hours, with extremes of two hours and ninety-six hours.

Thirty-six patients, of whom 7 had bacteremia, were successfully treated with one dose of serum. In these, crisis occurred on the average in ten hours. The average single successful dose was 279,000 units.

Serum sickness developed in 9 cases.

Forty-four patients recovered, and 2 died. The mortality rate for type VII pneumococcus pneumonia was 4.4 per cent.

Pneumonia Due to Pneumococcus Type VIII.—Thirty-eight patients with type VIII pneumococcus pneumonia were treated with type VIII refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Nineteen of them were admitted to the service with consolidation of two or more lobes, and 10 of these had bilateral consolidation. Twelve patients had bacteremia. The pneumonia had been present for an average of eighty hours, with extremes of fifteen hours and three hundred and thirty-six hours, before rabbit serum was administered. In 22 cases the pneumonia had been present seventy-two hours or more before treatment (chart 2). The average amount of

rabbit serum given was 300,000 units. The temperature fell to normal in an average of twelve hours, with extremes of three hours and forty-eight hours.

Thirty-four patients, of whom 9 had bacteremia, were successfully treated with one dose of serum. In these patients crisis occurred in an average of ten hours. The average single successful dose was 269,000 units.

Serum sickness developed in 9 cases.

Thirty-eight patients recovered, and none died. Thus the mortality rate for type VIII pneumococcus pneumonia was 0 per cent.

Pneumonia Due to Pneumococcus Type XIV.—Nineteen patients with type XIV pneumococcus pneumonia were treated with type XIV refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Five patients had consolidation of two or more lobes, and 3 of these had bilateral consolidation. Three patients had bacteremia. The pneumonia had been present for an average of one hundred and eleven hours, with extremes of thirty hours and one hundred and ninety hours, before rabbit serum was administered. In 16 cases the pneumonia had been present seventy-two hours or more before treatment was started (chart 2). The average amount of rabbit serum given was 333,000 units. The temperature fell to normal in an average of thirty-six hours, with extremes of eight hours and one hundred and twenty hours.

Twelve patients were successfully treated with one dose of serum, and in these crisis occurred in an average of twenty-three hours. The average single successful dose was 263,000 units.

Serum sickness developed in 8 patients.

Eighteen patients recovered, and 1 died. The mortality rate for type XIV pneumococcus pneumonia was 5.3 per cent.

COMPLICATIONS AND PREEXISTING DISEASES

Empyema occurred in 23 cases, and in 6 it was present at the time of admission to the hospital. Surgical drainage was required in 11 cases. Serum therapy produced spontaneous resolution in 8 cases. In 4 cases there was a fatal outcome.

Of those cases in which there were complications, delirium occurred in 20, jaundice in 10, noninfected pleural exudate in 16, otitis media in 7, meteorism in 7, pulmonary edema in 5, multiple pulmonary abscesses in 2, pulmonary atelectasis in 2, pericarditis in 2, meningismus in 4, circulatory collapse in 3 and gastroenteritis in 1.

There were preexisting diseases in 75 cases. Heart failure due to various causes occurred in 20, arteriosclerosis in 2, coronary occlusion in 2, hypertension in 2, uremia in 5, cystitis in 1, tuberculosis in 11, asthma in 7, bronchiectasis in 1, emphysema in 1, syphilis in 12, Hodgkin's disease in 1, diabetes in 2, diabetic acidosis in 1, hyper-

TABLE 2.—*Analysis of Deaths*

Sex	Race	Age	Lobes Involved	Bacter- emia	Preexisting Diseases and Complications	Interval Between Onset and First Dose of Serum, Hours	Total Dose of Serum, Units	Number of Doses	Comment
					Type I				
M	N	27	Right upper, right lower	+	Multiple pulmonary abscesses	126	200,000	1	
M	N	49	Left upper, left lower	+	Meteorism	94	310,000	2	Meteorism uncontrollable
M	W	62	Right upper, right lower	+	Arteriosclerosis of coronary arteries; auricular fibrillation	168	200,000	1	
M	W	40	Left upper, left lower	0	Empyema; pericarditis; uremia	76	510,000	3	
M	W	67	Right upper, right mid- dle, right lower	+	Hypertensive heart disease; auricular fibrillation; uremia; jaundice; empyema	72	1,080,000	3	Survival for 8 days after first dose of serum; death apparently from preexisting diseases
F	W	38	Right upper, right middle	+	Delirium	100	800,000	2	Death from massive pulmonary col- lapse 4 days after first dose of serum
F	W	45	Right lower	+	70	260,000	1	Temperature normal for 26 hr. after first dose of serum; sudden death
M	W	58	Left upper, left lower	0	Multiple pulmonary abscesses; coronary occlusion	104	300,000	1	Death apparently from coronary occlusion
M	W	65	Left lower	+	General arteriosclerosis; empyema; uremia	60	600,000	2	
					Type II				
M	W	43	Right lower, right middle	+	Pulmonary edema	146	300,000	1	Death from circulatory failure which was present when patient admitted to hospital
M	W	54	Right lower	+	Empyema	168	800,000	4	
F	N	35	Right lower	0	Hyperthyroidism; thyroid crisis	120	540,000	2	Death apparently from thyroid crisis
					Type VII				
M	N	62	Right upper, right mid- dle, right lower	+	Jaundice; delirium	96	500,000	2	
M	W	62	Right upper	+	Obesity; arteriosclerosis of coronary arteries; pul- monary edema	141	400,000	1	
					Type XIV				
F	W	45	Left lower	+	120	400,000	1	

thyroidism in 2, pregnancy in 4, cirrhosis of the liver in 1, anemia in 2, purpura haemorrhagica in 1, atrophic arthritis in 1, fractures in 4, epilepsy in 1 and delirium tremens in 2.

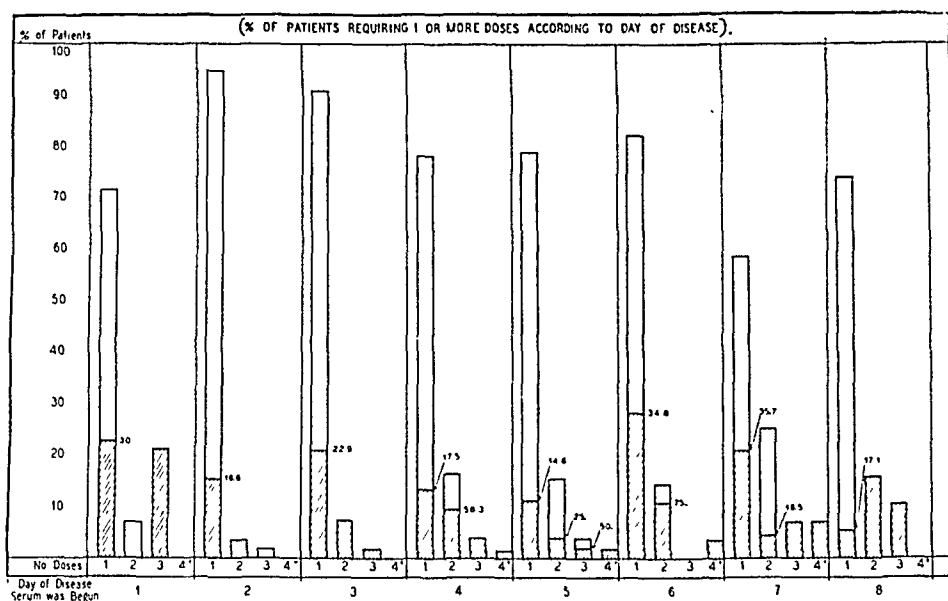


Chart 3.—Number of doses of homologous rabbit antipneumococcus serum required in 320 cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia. The diagonal lines and the figure at the right of each column represent the percentage of incidence of bacteremia.

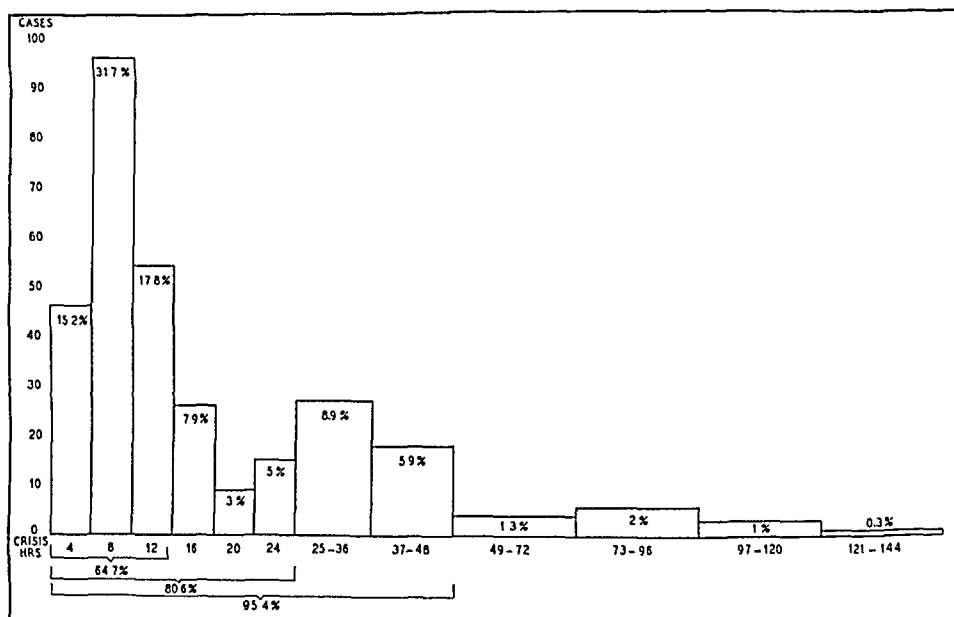


Chart 4.—Three hundred and three cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia in which recovery was by crisis.

ANALYSIS OF DEATHS

The 15 deaths are analyzed in table 2.

ANALYSIS OF RESULTS

It was possible to administer safely to each of the 320 patients a projected dose of refined and unconcentrated rabbit antipneumococcus serum. Two hundred and fifty-two, or 79 per cent, were successfully treated with this single predetermined dose (chart 3), and bacteremia was controlled in all but 3.

A rapid return to normal of the temperature, the pulse rate and the respiratory rate was usually observed, and of the 303 patients who recovered by crisis, 64.7 per cent had a normal temperature within twelve hours after serum therapy was begun and 80.6 and 95.4 per cent had normal temperatures within twenty-four and forty-eight hours respectively (chart 4).

No patients died when treated during the first two days of the disease, whereas the mortality rates in those first treated on the third, fourth, fifth, sixth and seventh days, were 7.5, 5.6, 5.9, 6.9 and 8.7 per cent respectively.

The mortality rate for the 320 patients, including 86 with bacteremia, was 4.7 per cent. In the group with bacteremia, there were 12 deaths: 7 from type I pneumococcus pneumonia, 2 from type II, 2 from type VII, and 1 from type XIV. The mortality rate of the patients with bacteremia was 13.9 per cent.

In the group without bacteremia, there were 3 deaths: 2 from type I pneumococcus pneumonia and 1 from type V. The mortality rate for the patients without bacteremia was 1.3 per cent.

Serum Reactions.—Chills following the administration of the rabbit serum occurred in 63 per cent of the cases. Although in a few instances such reactions were severe, they were never alarming. A rise of temperature, usually of 2 or 3 degrees (F.), followed the chills. This occurred generally after the first or second dose. The severity and the likelihood of occurrence diminished with subsequent doses. The occurrence and severity of the chills apparently were not dependent on the quantity or lot of serum used. Patients receiving large doses had chills no more frequently and no more severely than those receiving smaller doses. All patients receiving serum of the same lot did not have chills.

In a few instances anaphylactoid symptoms were noted. These were mild and did not cause alarm.

In 1 case the heart rate rose, the blood pressure fell 30 mm. of mercury and urticaria developed. In another case circulatory collapse occurred during the administration of the serum. After the intravenous injection of 2 minims (0.12 cc.) of epinephrine hydrochloride solution (1:1,000), the blood pressure returned to its previous level and serum therapy was continued. In 8 cases urticaria occurred during or shortly after the administration of serum.

Serum sickness developed in 31 per cent of the cases and was attended by the usual manifestations of fever, urticaria and arthritis. There were no instances of circulatory collapse during serum sickness.

SUMMARY AND COMMENT

Refined and unconcentrated rabbit antipneumococcus serum was found by us to be relatively nontoxic and effective in the treatment of types I, II, V, VII, VIII and XIV pneumococcus pneumonia.

When a projected dose was administered, an abundant supply of antipneumococcic substances was always made immediately available to the patient. A single projected dose produced a crisis in 252 (79 per cent) of the 320 cases. One hundred and ninety-six (65 per cent) and 244 (81 per cent) respectively of the 303 patients that recovered by crisis had normal temperatures within twelve and twenty-four hours after starting serum therapy.

The patients in our series were studied during periods when pneumonia was severe and when the incidence of bacteremia was high. The mortality rates obtained by us with rabbit antipneumococcus serum were lower than the majority of those for patients with milder pneumonia treated recently with chemotherapeutic substances.

Finland, Lowell and Strauss⁹ analyzed the deaths among their drug-treated patients according to seasons. The mortality rate for 382 patients treated with sulfapyridine, including those treated with serum, in the season of 1939-1940 was 12.6 per cent, whereas the mortality rate for 354 patients treated during the season of 1938-1939 was 20 per cent.

The mortality rate for our group of 320 patients treated with serum from Dec. 1, 1937, to April 30, 1939, although including 27 per cent with bacteremia, was 4.7 per cent. The mortality rate for the patients with bacteremia was 13.9 per cent, and for those without bacteremia, 1.3 per cent.

Flippin, Schwartz and Reinhold¹⁰ and Finland, Lowell and Strauss⁹ have reported large series of cases in which treatment with chemotherapeutic agents yielded satisfactory results. Flippin and associates stated that serum was used in those cases in which treatment with a drug failed to bring about a satisfactory clinical response within thirty-six to forty-eight hours. They felt that the serum was a deciding factor in the recovery of several patients. Finland and co-workers used specific

9. Finland, M.; Lowell, F. C., and Strauss, E.: Some Aspects of Chemotherapy of Pneumonia, *New York State J. Med.* **40**:1115 (July 15) 1940.

10. Flippin, H. F.; Schwartz, L., and Reinhold, J. G.: Sulfapyridine and Sulfathiazole Therapy in Pneumococcic Pneumonia, *J. A. M. A.* **116**:683 (Feb. 22) 1941.

serum for the patients with severe pneumonia who were treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfathiazole (2-[sulfanilamido]-thiazole).⁹

In view of these facts, we feel that rabbit antipneumococcus serum plays a definite part in the treatment of pneumococcic pneumonia and should not be discarded as an obsolete therapeutic agent until the chemotherapeutic agents are proved equally efficacious during periods of severe pneumonia when there is a high incidence of bacteremia. The treatment of pneumonia in the future, however, will probably progress to the combined use of drugs and specific serum.

Drs. Joseph K. Bradford, Duncan Clark, John Conley, Robert Dickes, Henry Gardstein, Philip Grenley, Ernest E. Keet, Catherine D. Mangan, Albert H. Meyer, David Rabinowitz and Sanford Sarney gave clinical assistance.

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Progress in Internal Medicine

METABOLISM AND DIABETES

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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GLYCOGEN AND CARBOHYDRATE METABOLISM

In last year's review the importance of the work of Cori and his associates¹ on the synthesis of glycogen in vitro by the action of an enzyme called phosphorylase was pointed out. Phosphorylase, which is found in liver and muscle extracts and in yeast, acts on dextrose and phosphoric acid in the presence of adenylic acid, which acts as a coenzyme. Cori proceeded further in this investigation and in a recent paper² outlined the steps in the metabolism of glycogen as follows: 1. Glycogen plus phosphoric acid in the presence of the glycogen phosphorylase found in liver and other tissue yields dextrose-1-phosphate. This is a reversible reaction. 2. Dextrose-1-phosphate in the presence of phosphoglucomutase, an enzyme which is found in all tissue extracts, yields dextrose-6-phosphate. This reaction is irreversible. 3. Dextrose-6-phosphate in the presence of isomerase, an enzyme which is found in all tissue extracts, yields fructose-6-phosphate. Cori further stated that when this particular reaction has reached a state of equilibrium, the two esters are present in the proportion of 80 per cent dextrose and 20 per cent fructose. Such a mixture is known as hexosemonophosphate, or equilibrium ester. 4. Dextrose-1-phosphate or dextrose-6-phosphate when added to liver extract yields dextrose and inorganic phosphate through the action of phosphatase in the liver. These steps, Cori stated, are those taken in the formation of blood sugar.

From the Division of Medicine (Dr. Ryneerson), the Mayo Clinic.

1. Cori, C. F.; Schmidt, G., and Cori, G. T.: The Synthesis of a Polysaccharide from Glucose-1-Phosphate in Muscle Extract, *Science* **89**:464-465 (May 19) 1939. Cori, G. T.; Cori, C. F., and Schmidt, G.: The Rôle of Glucose-1-Phosphate in the Formation of Blood Sugar and Synthesis of Glycogen in the Liver, *J. Biol. Chem.* **129**:629-639 (Aug.), 1939.

2. Cori, C. F.: Symposium on Carbohydrate Metabolism: Glycogen Break-down and Synthesis in Animal Tissues, *Endocrinology* **26**:285-296 (Feb.) 1940.

Results of this series of investigations suggested that the enzymes concerned in the breakdown and the synthesis of glycogen in the liver and elsewhere play a fundamental role in carbohydrate metabolism. According to Cori, such an enzymatic breakdown leads to the formation of blood sugar in the liver and of lactic acid in muscle. In addition, various substances, including insulin, epinephrine, adrenocortical hormone, the active principles of the adrenal cortex and of the anterior lobe of the pituitary gland and possibly the sex hormones, influence enzyme activity in the cells and may thus play an important role in carbohydrate metabolism.

Janes and Nelson³ reported that the administration to rats of 0.05 mg. of stilbestrol twice daily for five to twenty days resulted in elevation of the level of blood sugar and considerable rise in the glycogen content of the liver, although the glycogen content of muscle was not similarly increased. They expressed the opinion that both fat and protein serve as sources of the additional carbohydrate and that the stilbestrol might have produced such an effect through the adrenal glands, the gonads or both.

Studies on the effect of the adrenal glands, particularly the adrenal cortex, on carbohydrate metabolism have been numerous in the past few years. Recently, Long and his co-workers⁴ stated:

The injection of cortical extract or certain crystalline steroids isolated from the adrenal cortex into fasted adrenalectomized and normal rats and mice elevates the liver glycogen from ten to forty fold, resulting in levels far beyond those encountered in normal untreated animals. The blood glucose is also significantly increased, but no effects were observed on the muscle glycogen level.

They further reported that in depancreatized animals, the quantity of sugar in the urine, previously reduced by adrenalectomy, could be increased by cortical extract. They found a similar "diabetogenic" effect of cortical extract on fasting hypophysectomized depancreatized rats. Corticosterone and dehydrocorticosterone were found to exert marked effects on both carbohydrate and electrolyte metabolism, while desoxycorticosterone and progesterone, although capable of influencing both the duration of life and the electrolyte balance of adrenalectomized animals, had only a comparatively feeble effect on carbohydrate metabolism. They concluded that the "cortical hormone stimulates those processes of gluconeogenesis by which the blood glucose is maintained at the expense of the tissue proteins."

3. Janes, R. G., and Nelson, W. O.: Effect of Stilboestrol on Certain Phases of Carbohydrate Metabolism, *Proc. Soc. Exper. Biol. & Med.* **43**:340-342 (Feb.) 1940.

4. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, *Endocrinology* **26**:309-344 (Feb.) 1940.

On the other hand, Seckel ⁵ reported that glycogenolysis in the liver of rats, as it proceeded in sliced tissue suspended in a buffered salt solution, was inhibited by adrenal cortex extract added *in vitro*. He concluded that one essential function of the cortical hormone could consist in inhibition of the glycogenolytic enzyme of the liver cells. Furthermore, Russell ⁶ reported that in normal rats fed dextrose both whole anterior pituitary extract and adrenal cortical extract appeared to depress the utilization of carbohydrate and to promote deposition of glycogen. The former increased the muscle glycogen, and the latter more markedly affected the stores in the liver. She concluded that anterior pituitary extract and adrenal cortex extract have a synergistic, as well as, in part, a complementary, action on the metabolism of dextrose fed to rats.

Controversy continues with regard to the disturbance in carbohydrate metabolism primarily concerned in diabetes mellitus. Soskin ⁷ supported the so-called overproduction theory. He stated that in diabetes the ketone bodies as well as the blood sugar are capable of utilization by the extrahepatic tissue, but that they are produced by the liver at rates which exceed the power of the tissue to dispose of them. He ⁷ reported that the completely depancreatized dog receiving a constant injection of insulin sufficient to maintain a normal level of blood sugar has a normal dextrose tolerance curve, including the Straub-Traugott phenomenon and the hypoglycemic phase. On the other hand, a hepatectomized dog with an intact pancreas which received a constant injection of dextrose sufficient to maintain a normal level of blood sugar invariably has a diabetic tolerance curve. From these results, he concluded that the pancreas is not essential to the metabolic reactions which determine the normal dextrose tolerance curve, while the normal liver is essential. In the presence of sufficient insulin, the normal liver, as one of its responses to administered dextrose, decreases the output of sugar to the blood, which it had previously been supplying from its own resources. The stimulus which elicits the hepatic inhibitory response is the blood sugar itself, and the threshold of stimulation of the hepatic mechanism in a particular animal depends, Soskin claimed, largely on the endocrine balance. This balance may consist of the opposing influences of the hormones of the pancreas and the anterior lobe of the pituitary. When

5. Seckel, H. P. G.: The Influence of Various Physiological Substances on the Glycogenolysis of Surviving Rat Liver: Influence of Cortical Hormone Added *in Vitro*, *Endocrinology* **26**:97-101 (Jan.) 1940.

6. Russell, J. A.: The Relationship of the Anterior Pituitary and the Adrenal Cortex in the Metabolism of Carbohydrate, *Am. J. Physiol.* **128**:552-561 (Feb.) 1940.

7. Soskin, S.: The Liver and Carbohydrate Metabolism, *Endocrinology* **26**: 297-308 (Feb.) 1940.

insulin is lacking or when an excess of anterior pituitary hormones is present, the liver threshold, or the blood sugar level at which the inhibitory response is manifested, rises, and hyperglycemia results. An excess of insulin or a deficiency of the anterior pituitary hormones, on the other hand, lowers the liver threshold, and hypoglycemia results. When both insulin and the anterior lobe of the pituitary are lacking, as in the Houssay animal, the diabetes is ameliorated, and most of the criteria of normal carbohydrate metabolism are fulfilled.

Thannhauser,⁸ however, disagreed with Soskin's theory that increased glyconeogenesis in cases of diabetes is the primary reason for the disturbance. He stated that if this were true, all diabetic patients would exhibit an increased minimal excretion of nitrogen, since the additional carbohydrate would come, at least in part, from protein catabolism. He reported that in 4 cases of moderately severe diabetes in which a minimal nitrogen diet was employed the minimal excretion of nitrogen was normal even though insulin was temporarily omitted. In 3 cases of severe diabetes in which a similar diet was given, the minimal excretion of nitrogen was slightly increased; simultaneously, large concentrations of sugar, four to seven times more than the amounts anticipated from the increased figures for the minimal excretion of nitrogen, appeared in the urine. Irradiation of the pituitary gland produced only a slight and temporary depression of the minimal excretion of nitrogen, while injection of extracts of whole pituitary and of adrenal cortex had no influence at all. Thannhauser concluded that the primary disturbance in diabetes mellitus consists in a partial failure of the molecule of sugar to be disintegrated in intermediary metabolism, that glyconeogenesis is the result of, and not the primary factor in, the mechanism of diabetes and that insulin does not act directly on glyconeogenesis but exerts its influence on the intermediary disintegration of sugar.

Several investigators emphasized the importance of stores of glycogen in the liver. Richardson⁹ reported that in both normal rabbits and depancreatized cats survival after intravenous inoculation with bacteria was increased by high carbohydrate diets, which raised the glycogen content of the liver. Dissemination of bacteria from an intradermal focus in depancreatized cats, he reported, seemed to be correlated with alterations in glycogen in the skin, was increased by acidosis and occurred with a greater frequency in diabetic cats than in control animals. On the other hand, this dissemination could not be correlated with

8. Thannhauser, S. J.: Studies on the Mechanism of Diabetic Disturbance Using the "Nitrogen Minimum Excretion" as a Measure of Glyconeogenesis, *Endocrinology* **26**:189-200 (Feb.) 1940.

9. Richardson, R.: Immunity in Diabetes: III. Relation of Tissue Glycogen and Blood Chemistry to Bacterial Dissemination, Antibody Formation and Survival After Infection in Diabetes, *J. Clin. Investigation* **19**:239-250 (Jan.) 1940.

alterations in the amount of sugar in the blood, cholesterol or protein in the serum or glycogen in the liver.

Messinger and Hawkins¹⁰ reported that in dogs in which the liver had been damaged previously with sufficient arsphenamine to produce jaundice, a diet high in carbohydrate or in protein aided in the restoration of hepatic function. Such a diet given before or during the administration of arsphenamine protected the liver from damage.

DIABETES MELLITUS

Incidence and Mortality.—Discussions continue on the increase or decrease in the incidence of diabetes. The general consensus is that the incidence of diabetes mellitus actually is increasing throughout the world. Beek and Groen¹¹ published the results of a detailed study in regard to the mortality rate of diabetes mellitus in the Netherlands. It increased tremendously from 1903 to 1937; in 1903, 424 persons died of this disease, and in 1937, 1,637. During these years the total population increased from 5,500,000 to 8,500,000. At present the mortality rate of diabetes in the Netherlands is one of the highest in the world; in 1935 it was surpassed only by those in the United States, Prussia, the Union of South Africa and Denmark. This increase in the mortality rate of diabetes is in sharp contrast to the marked decrease in the general mortality rate in the Netherlands, which fell during the period from 1903 to 1937 from 15.58 per thousand to 8.78 per thousand. Beek and Groen considered the causes which may have contributed to this increase and, while recognizing that the improved diagnosis of the disease and other factors may have contributed, they concluded that the increase is real and not apparent. They questioned if this increase may not be attributable to improved standards of nutrition and to decreased amounts of physical exercise. This increase in the mortality rate has taken place almost exclusively among those more than 50 years of age. The mortality among younger persons has decreased with the use of insulin. The higher mortality rate found in the cities may be due to the proportionately higher percentage of Jews. Diabetes has increased not only as a principal cause of death but as a contributory cause or complication. The most common complications are cardiac disease, angina pectoris, apoplexy, furunculosis and gangrene. The mortality rate among diabetic patients with pulmonary tuberculosis has decreased greatly. The mortality rate of diabetes itself, as well as the mortality rate of

10. Messinger, W. J., and Hawkins, W. B.: Arsphenamine Liver Injury Modified by Diet, Protein and Carbohydrate Protective, but Fat Injurious, *Am. J. M. Sc.* **199**:216-225 (Feb.) 1940.

11. Beek, E. S., and Groen, J.: The Mortality from Diabetes Mellitus in the Netherlands: Medical-Statistical Study, *Geneesk. bl. u. klin. en lab. v. d. prakt.* **37**:187-225, 1939.

diabetic coma, has remained rather constant since 1936. More than 200 patients die of diabetic coma in the Netherlands every year.

Joslin¹² long has been interested in the incidence of diabetes in various parts of the world and in various parts of the United States. After a detailed study of the incidence of the disease in Arizona, he concluded that diabetes is universal and found no evidence that the incidence is less in Arizona than elsewhere. This observation is important because of the discussions in regard to the influence of the seasons on the severity of diabetes and its complications. Owens and Mills¹³ studied this problem in Cincinnati. They divided the year into seven months of winter (October to April) and five months of summer and found that more diabetic patients were admitted to hospitals for treatment of arteriosclerotic conditions in the winter than in the summer. The number of diabetic patients admitted to hospitals in the winter for other than arteriosclerotic conditions did not vary significantly from the number admitted in the summer.

Gangrene far outranked all other sclerotic complications. Less than a third of the patients who were admitted to hospitals because of diabetes had sclerotic complications. Owens and Mills concluded that there was no evidence of seasonal effect on the severity of diabetes not complicated by sclerotic conditions. They cited the observations of Beard,¹⁴ of Minneapolis, who found that in 95 per cent of cases of diabetic gangrene this complication developed during the winter months. According to them, Blotner and Fitz¹⁵ of Boston and Paullin¹⁶ of Atlanta, Ga., also agreed that the incidence of gangrene increased during colder weather. Owens and Mills also cited Joslin as expressing the belief that the factors which contributed to the higher incidence during the winter were poor hygiene of the feet, increased spasm of the vascular system and decreased blood flow. Pannhorst and Rieger¹⁷ concluded that in spite of seasonal correlations diabetes mellitus cannot be regarded as a seasonal disorder. Escudera, cited by Ryberg,¹⁸ stated that there was a striking difference

12. Joslin, E. P.: The Universality of Diabetes: A Survey of Diabetic Morbidity in Arizona, *J. A. M. A.* **115**:2033-2038 (Dec. 14) 1940.

13. Owens, L. B., and Mills, C. A.: Influence of Season on the Severity of Diabetes and Its Sclerotic Complications, *Am. J. M. Sc.* **199**:705-708 (May) 1940.

14. Beard, A. H.: Treatment of Gangrene in Arteriosclerotic Diabetes, *Minnesota Med.* **8**:436-439 (July) 1925.

15. Blotner, H., and Fitz, R.: On Diabetic Gangrene, with Particular Reference to the Value of Insulin in Its Treatment, *Boston M. & S. J.* **194**:1155-1162 (June 24) 1926.

16. Paullin, J. E., in discussion on papers of Warfield and Lemann, *J. A. M. A.* **89**:662 (Aug. 27) 1927.

17. Pannhorst, R., and Rieger, A.: Manifestierung des Diabetes und Jahreszeit, *Ztschr. f. klin. Med.* **134**:154-161 (May 21) 1938.

18. Ryberg, P. E.: Personal communication to the authors.

in the incidence of diabetes in the Argentine. The incidence is lower in the north, where the climate is stable, than in the south, where the climate is less stable. The impression that the low incidence of diabetes in the southern part of the United States is explained by incomplete statistics seems not to apply in the Argentine since the standards of medical practice in the northern part of that country are high.

The Department of Health of Pennsylvania¹⁹ recently announced new regulations by which both cancer and diabetes become reportable diseases. Previously, diabetes was registered only at the time of death. This improved method of reporting, if applied in all states, would benefit statistical analyses materially.

The Metropolitan Life Insurance Company²⁰ reported that the mortality rate of diabetes in the United States has resumed an upward trend after a temporary rest. In the first part of 1940 there was an increase of 13 per cent over the same period for 1939. The mortality rate among patients less than 25 years of age is low, only 1 or 2 per hundred thousand. This low rate, of course, is due to the use of insulin. As a matter of fact, it is only among patients more than 65 years of age that the mortality rates have increased steadily and rapidly. Since the population as a whole includes a steadily increasing percentage of older persons, a correction should be made in the mortality rates for diabetes. When this correction is made, the rise in the mortality rate for all ages is much more moderate. Regardless of any such correction, the known incidence of the disease has increased much faster than the mortality rate. There are no exact figures, but there are probably 500,000 to 600,000 cases of diabetes in the United States. Some estimates are even higher, and it is not unlikely that at the end of the present decade the figure will reach 1,000,000. If the mortality rate was computed on the basis of the diabetic population, rather than on the basis of the general population, it would probably show a decrease. Statistics from the Baker Clinic computed on the former basis disclosed an improvement in the mortality rate among diabetic patients of practically every age group, especially among children. It is encouraging to know that the mortality rate of diabetic coma has been reduced greatly. Even the mortality rates of other conditions, such as gangrene, to which an older person with diabetes is particularly susceptible, have been decreased. Most diabetic patients die of another disease common to their age group, such as cardiovascular disease, cancer or pneumonia. Many deaths could be prevented by education of those persons who have a family history of diabetes and are themselves overweight.

19. Cancer and Diabetes Made Reportable, *Medical News*, J. A. M. A. **112**:755 (Feb. 25) 1939.

20. The Outlook for Diabetes in the 1940's, *Statist. Bull. Metrop. Life Ins. Co.* **21**:5-8 (May) 1940.

Hereditary Factors.—Identical twins have long been a source of interest in studying the hereditary factor in diabetes. Fischer ²¹ reported the cases of identical twins, now 8½ years of age. Diabetes developed in 1 at 4 years of age; the other twin is entirely normal and has a normal sugar tolerance curve. It will be interesting to have a further report on these twins. The genetic aspect of diabetes mellitus in Germany ²² was studied in an unselected group of twins. There were 411 pairs of twins among 85,000 diabetic patients. Of these 411 pairs, 46 were enzygotic and 87 were dizygotic. As a result of the study, the conclusion was drawn that diabetes mellitus is purely hereditary.

Traumatic Factors.—In an editorial ²³ in which the causal relation of trauma to diabetes was discussed and the literature was reviewed, the general conclusion was drawn that there is no evidence of trauma itself causing diabetes but that it may cause latent diabetes to be manifest.

Diagnosis.—The diagnosis of diabetes mellitus by sugar tolerance curves is necessary in many instances. Matthews, Magath and Berkson ²⁴ made a study of the one hour—two dose dextrose tolerance test (Exton-Rose procedure). As a result of this study, they concluded that the final one hour blood sugar reading is far more significant than any curves which may be drawn. They found that 95 per cent of diabetic patients had a blood sugar reading of 158 mg. or more per hundred cubic centimeters at the end of an hour. They felt that whenever the value for blood sugar was 180 mg. at the end of an hour, a diagnosis of diabetes mellitus should be regarded as certain; if the value was 154 mg. or less, the diagnosis of diabetes should not be made. Tunbridge and Allibone ²⁵ discussed the intravenous dextrose tolerance test, which they preferred to the usual test in which the dextrose is administered orally. Robinson and Shelton ²⁶ reported a variation in sugar tolerance curves in cases of nervous and mental disease and called attention to the fact that conditions other than diabetes mellitus may affect the sugar tolerance curve.

21. Fischer, A. E.: Diabetes Mellitus in One of Identical Twins, *Am. J. Dis. Child.* **59**:386-393 (Feb.) 1940.

22. The Genetic Aspect of Diabetes Mellitus, *Foreign Letters (Berlin)*, J. A. M. A. **112**:1091 (March 18) 1939.

23. Trauma and Diabetes, editorial, J. A. M. A. **112**:1592-1594 (April 22) 1939.

24. Matthews, M. W.; Magath, T. B., and Berkson, J.: The One Hour—Two Dose Dextrose Tolerance Test (Exton-Rose Procedure): Diagnostic Significance, J. A. M. A. **113**:1531-1537 (Oct. 21) 1939.

25. Tunbridge, R. E., and Allibone, E. C.: The Intravenous Dextrose Tolerance Test, *Quart. J. Med.* **9**:11-35 (Jan.) 1940.

26. Robinson, G. W., Jr., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients: A Study of Sixty-Nine Successive Admissions; Preliminary Report, J. A. M. A. **114**:2279-2284 (June 8) 1940.

Fabrykant and Wiener²⁷ expressed the belief that examination of the urine for three days after the dextrose tolerance test is performed is even more useful than the test itself in determining actual tolerance to carbohydrate.

Wheelon²⁸ described the paradoxical response of blood sugar of 40 patients to ingested dextrose; the blood sugar level of 20 was 70 mg. or less per hundred cubic centimeters during the course of the dextrose tolerance test. Conn²⁹ emphasized the necessity of a standard preparatory diet with an adequate intake of carbohydrate before performance of a dextrose tolerance test, for if the intake has been restricted a false positive curve may be obtained. This observation has been noted repeatedly among patients who have been undernourished or who have undergone surgical operations. Conn's statements were most timely. As a matter of fact, a sugar tolerance curve which is not definitely positive should be regarded with suspicion, and the test should be repeated and the result reevaluated at a later date. Extreme caution should be exercised in interpretation of the sugar tolerance curve of patients suspected of having hypoglycemia, because, as has been mentioned, there are many patients whose concentration of blood sugar drops to less than normal when this test is performed. The use of the sugar tolerance curve in the diagnosis of hypoglycemia was discussed by Conn.³⁰

Associated Pregnancy.—In 1939, Smith and Smith³¹ reported their observations on 173 pregnant women. They expressed the opinion that the eclamptic toxemias are characterized by an excessive amount of gonadotropin in the serum and that its occurrence precedes the clinical signs of toxemia by approximately four to six weeks. This change failed to appear in about 12 per cent of the women studied. The increase of gonadotropin in the serum was not present in cases of nephritic or hypertensive toxemia. They suggested that premature delivery is sometimes associated with such excess. The findings in the group of pregnant diabetic women studied followed the same pattern. The authors were inclined to explain the phenomenon as due to failure of the

27. Fabrykant, M., and Wiener, H. J.: The Effect of Added Carbohydrate upon Stabilized Insulin-Treated Diabetics, *Am. J. M. Sc.* **199**:834-840 (June) 1940.

28. Wheelon, H.: Reverse or "Paradoxical" Blood Sugar Response to Ingested Glucose: A Correlation of Laboratory and Clinical Findings on Forty Patients, *Endocrinology* **26**:743-752 (May) 1940.

29. Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, *Am. J. M. Sc.* **199**:555-564 (April) 1940.

30. Conn, J. W.: The Spontaneous Hypoglycemia: Importance of Etiology in Determining Treatment, *J. A. M. A.* **115**:1669-1675 (Nov. 16) 1940.

31. Smith, G. Van S., and Smith, O. W.: The Anterior Pituitary-Like Hormone in Late Pregnancy Toxemia: A Summary of Results Since 1932, *Am. J. Obst. & Gynec.* **38**:618-624 (Oct.) 1939.

body to use the gonadotropin in the production of increased amounts of the estrogen and progestin steroids, which are normally characteristic of pregnancy.

White and her associates³² at the Baker Clinic had a most unusual opportunity to study pregnancy in diabetic women. They called attention to the fact that, unlike other complicating diabetic situations, the continued use of insulin did not solve the problem of pregnancy in diabetes. Until recently, it has been nearly as true of the insulin era as of the period before that only every other pregnancy in a diabetic woman terminated successfully. Accidents of such pregnancies do not concern the welfare of the mother, for the maternal mortality rate is low, but they do concern the welfare of the child and result in (1) early spontaneous abortion, miscarriage or premature birth, (2) stillbirth or (3) a neonatal type of death common within twenty-four hours after delivery. They^{32b} studied 353 instances of pregnancy among 242 diabetic women encountered since 1898; they included patients whom they treated during pregnancy and those treated elsewhere during that period and seen by them at a later date. Excessive fetal mortality rates have been reported by them and by all other investigators. Excluding those cases in which pregnancy was interrupted by cesarean section, the fetal mortality rate before insulin was introduced was 44 per cent and that after the introduction of insulin 38 per cent. Before the use of insulin, the early and late fetal deaths occurred with equal frequency. Since insulin has been used, 60 per cent of the deaths were late and were due to stillbirth or to a neonatal accident and 40 per cent were attributable to spontaneous abortion. It is much easier to study the problems of late pregnancy than those of early pregnancy because most women come for examination late.

Although for years these neonatal accidents have been attributed to diabetes itself, its complications or its treatment, the authors expressed the opinion that there is now evidence to suggest that these accidents are not due to faulty treatment or to poor control of the diabetes. They noted that even severe coma or hypoglycemia was not incompatible with the life of the child and that these accidents often occurred among the patients under good control, while the pregnancies of some careless patients terminated successfully. Hence, the authors suggested that some "extradiabetic" factor must be sought in order to explain these deaths.

The first suggestion that pregnant diabetic patients may have a hormonal imbalance was made in 1933 by Murphy,³³ who found that

32. (a) White, P., and Hunt, H.: Prediction and Prevention of Pregnancy Accidents in Diabetes, *J. A. M. A.* **115**:2039-2040 (Dec. 14) 1940. (b) White, P.; Titus, R. S.; Joslin, E. P., and Hunt, H.: Prediction and Prevention of Late Pregnancy Accidents in Diabetes, *Am. J. M. Sc.* **198**:482-492 (Oct.) 1939.

33. Murphy, D. P.: The Excretion of Ovary Stimulating Hormone in the Urine During Pregnancy, *Surg., Gynec. & Obst.* **56**:914-917 (May) 1933.

excessive amounts of gonadotropin were excreted in the urine of 2 pregnant diabetic women. Smith and Smith ³⁴ found a high incidence of preeclamptic toxemia among diabetic patients. White and her associates, therefore, expressed the opinion that stillbirth and other accidents of this type in their patients were more likely to be related to an abnormal hormonal picture than to any of the other factors described previously. They found that among many diabetic patients the course of pregnancy was uneventful until the sixth month and that thereafter edema, albuminuria and high blood pressure often developed. Shortly after the rise in blood pressure, the fetus died and signs of toxemia disappeared promptly. The entire clinical picture can appear and clear up within a week, but its onset is preceded by an increase in the gonadotropin in the serum ^{32b} over a period of four to six weeks. Between January 1936 and June 12, 1940, they studied 61 pregnant diabetic women and made several determinations of this principle in the serum throughout the term of each pregnancy. The studies were begun about the twenty-fourth week of pregnancy, and determinations were performed at intervals of five to seven days. Most of the patients had moderately severe to severe diabetes, but all were under adequate dietary and insulin control. In this group, coma developed in only 1 case and severe hypoglycemic shock in only 1. In neither instance was there any interference with the pregnancy. Twenty-five of the 61 patients had normal amounts of gonadotropin in the serum (less than 200 rat units per hundred cubic centimeters). All 25 had an uneventful pregnancy, without toxemia. No premature deliveries and no miscarriages occurred, and there were only 2 infant deaths, a survival rate of 92 per cent. One infant died of asphyxia pallida two hours post partum; necropsy revealed nothing of importance. The other infant died of hemorrhagic disease of the newborn several days post partum. Twelve of the 61 patients had abnormally high values for gonadotropin in the serum, and this value rose steadily until term. Complications developed among all of these patients during pregnancy. Nine had preeclamptic toxemia, and 3 had premature deliveries. All were placed in the hospital and treated routinely for this type of toxemia as soon as it appeared, but notwithstanding, the toxemia progressed. Three fetal deaths occurred within the uterus during the toxemic phase of the pregnancy, and 3 infant deaths occurred after premature delivery.

One diabetic patient had two successive pregnancies, associated with preeclamptic toxemia. The abnormally high values for gonadotropin in

34. Smith, G. Van S., and Smith, O. W.: Further Quantitative Determinations of Prolan and Estrin in Pregnancy, with Especial Reference to Late Toxemia and Eclampsia, *Surg., Gynec. & Obst.* **61**:27-35 (July) 1935; footnote 31.

the serum fell steadily during the last trimester. As the amount of this substance in the serum decreased, the toxic symptoms were reduced markedly in the first pregnancy and cleared up entirely in the second pregnancy; the symptoms were less severe in the second pregnancy. The decrease in the gonad-stimulating factor was preceded by an increase in estrogen.

Twenty-four of the patients in whose serum the amount of gonadotropin was abnormally high were given replacement therapy. Thirteen received this treatment in the form of estrogenic substance, 150,000 to 300,000 international units of estradiol benzoate (progynon B) given each day, as well as progestin in doses of 10 to 20 mg. Eleven of them received medication in the form of stilbestrol in doses of 40 to 120 mg. daily and pregnolinine in doses of 10 to 40 mg. daily. The progestin was administered because it had been demonstrated that the excretion of sodium pregnandiol glucuronidate had been lowered. In some instances, testosterone was substituted for the progestin. Although most of these patients had symptoms of preeclamptic toxemia associated with the elevated values for gonadotropin in the serum, including albuminuria, edema, hypertension, headache, nausea and vomiting, the treatment with estrogen or androgen was followed by a drop in the gonadotropin in the serum. Progressive toxemia and miscarriages did not occur; signs of improvement in the general condition, including lessening of the toxic symptoms, were noted. Only 1 fetal and 1 infant death occurred in this series. In the first case, in which the replacement therapy had been stopped because of the high cost of the estrogen, toxemia recurred and stillbirth resulted. In the other instance the infant died of erythroblastosis a day or so after birth.

It is of interest to note that even with administration of such massive doses of stilbestrol no side reactions and no demonstrable decrease in liver function were noted.

White and her associates^{32b} also studied the question of hypoglycemia of the infants of diabetic mothers. This subject has been reviewed by Randall and Ryneerson.³⁵ White and her co-workers stated that in their series of patients hypoglycemia developed but did not result in death of the infant. Only 10 of 127 blood sugar values were found to be within the hypoglycemic range. She and her co-workers expressed the opinion also that the large size of the baby was not related to the hyperglycemia^{32b} of the mother, but rather that it might be due to an imbalance of hormones. These papers have been reviewed in such detail because of their importance and because of the hope that others

35. Randall, L. M., and Ryneerson, E. H.: Delivery and Care of the New-Born Infant of the Diabetic Mother, *J. A. M. A.* **107**:919-924 (Sept. 19) 1936.

interested in this field will perform similar studies on similar patients. The facilities necessary for such a study and the high cost of the treatment as outlined by these authors may make this method difficult for many to attempt.

Helwig³⁶ studied the pancreases of 9 infants of diabetic mothers and 9 infants of nondiabetic mothers. The islands of Langerhans of the infants of diabetic mothers exhibited a variable degree of hyperplasia and hypertrophy. The authors concluded that "some infants of diabetic mothers have definitely larger amounts of insular tissue than infants of nondiabetic mothers." They reported but little correlation between the concentration of sugar in the infant's blood and the size of the islands of Langerhans. Miller and Ross³⁷ studied the relation of hypoglycemia to the symptoms observed among infants of diabetic mothers. The average value for blood sugar of 6 infants born to diabetic mothers was 29.7 mg. per hundred cubic centimeters, as compared with 31.8 mg. for 20 premature infants born to normal mothers and with 49.9 mg. for 17 full term infants born to normal mothers. The authors expressed the belief that there was no relation between the level of the blood sugar and an infant's symptoms and that the symptoms and the clinical course could in each instance be explained better on the basis of organic disease. Ketteringham³⁸ studied results of dextrose tolerance tests performed on newborn infants both of normal and of diabetic mothers. He found that infants and young adults responded to the tests in the same way. The tests were much more difficult to perform on the infants of diabetic mothers, and the results were less satisfactory, owing to technical factors.

Rosenthal³⁹ reviewed the entire subject of children born to diabetic mothers. He discussed the high mortality rate and the possible contributory factors, including gigantism, the higher incidence of congenital defects and hypoglycemia. He stated that it is important to undertake measures to prevent some of these unfortunate occurrences and suggested following one of three lines or a combination thereof: (1) adequate control of the mother's diabetes, (2) treatment with estrogen, as suggested by White, and (3) cesarean section in the thirty-sixth or thirty-seventh week, as suggested by Randall and one of us (E. H. R.).

36. Helwig, E. B.: Hypertrophy and Hyperplasia of Islands of Langerhans in Infants Born of Diabetic Mothers, *Arch. Int. Med.* **65**:221-239 (Feb.) 1940.

37. Miller, H. C., and Ross, R. A.: Relation of Hyperglycemia to the Symptoms Observed in Infants of Diabetic Mothers: Report of Six Cases, *J. Pediat.* **16**: 473-481 (April) 1940.

38. Ketteringham, R. C.: Dextrose Tolerance Tests of the Newborn, *Am. J. Dis. Child.* **59**:542-553 (March) 1940.

39. Rosenthal, R.: Children of Diabetic Mothers, editorial, *Minnesota Med.* **23**: 259-262 (April) 1940.

Juvenile Diabetes.—Barach,⁴⁰ Grishaw, West and Smith,⁴¹ and White⁴² discussed some of the problems of juvenile diabetes. Their articles are fairly typical of those which are being written on this subject, and only two comments need to be made: First, more and more diabetic children are leading perfectly normal lives and are developing in a perfectly normal fashion. This is due as much as anything to the fact that these children are more frequently given normal diets adequate in caloric, mineral and vitamin content. Diabetic dwarfism was seen much more frequently when diets low in content of calories and vitamins were prescribed. Diabetic children now are growing normally and should become useful citizens. The other comment is that many articles are being written suggesting that these diabetic children have an endocrine imbalance. Personally, we feel that there are too many unwarranted conclusions about this condition with not enough good evidence. Too many of these children are receiving injections of endocrine preparations of one type or another or, what is much worse, are being given them by mouth. While it is true that diabetic children may have a disturbance of some of the other endocrine glands, the only real facts available indicate that the only acknowledged deficiency is a deficiency of insulin and that many of these other changes are secondary to the disease rather than contributing factors to the production of the condition. No one has presented any convincing evidence that there is better treatment for the diabetic child than the accepted standardized procedure of an adequate diet and sufficient insulin for the control of the disease.

Pancreas and Organs of Secretion.—Among adults there has been a little better opportunity for studying the possible relation of the pancreas to other organs of internal secretion. Gessler and his associates⁴³ studied 5 diabetic women who had passed the menopause and who were treated with intramuscular injections of estradiol benzoate. Three of the 5 patients improved with estrogenic therapy. Spiegelman⁴⁴ reported also on the influence of estrogen on the insulin requirements of diabetic patients. He studied 9 diabetic patients for four months before estro-

40. Barach, J. H.: Growth in Diabetic Children, *Pennsylvania M. J.* **42**:1459-1467 (Sept.) 1939.

41. Grishaw, W. H.; West, H. F., and Smith, B.: Juvenile Diabetes Mellitus, *Arch. Int. Med.* **64**:787-799 (Oct.) 1939.

42. White, P.: Endocrine Manifestations in Juvenile Diabetes, *Arch. Int. Med.* **63**:39-53 (Jan.) 1939.

43. Gessler, C. J.; Halsted, J. A., and Stetson, R. P.: Effect of Estrogenic Substance on the Blood Sugar of Female Diabetics After the Menopause, *J. Clin. Investigation* **18**:715-722 (Nov.) 1939.

44. Spiegelman, A. R.: Influence of Estrogen on the Insulin Requirement of the Diabetic, *Proc. Soc. Exper. Biol. & Med.* **43**:307-308 (Feb.) 1940.

genic therapy was begun, for five months during its administration and for three months after its administration had been discontinued. He reported a variable decrease in the insulin requirements of the diabetic patients treated. It is interesting to note that the age of the patient was important. Surprisingly, among the premenopausal patients there was a daily saving of insulin of 63 per cent. Of the postmenopausal patients, there was a daily average saving of only 41 per cent. The authors did not state whether the decreased expense from the standpoint of the amount of insulin used was more than overbalanced by the increased expenditure for the estrogenic product. Cantilo⁴⁵ reported the results of his studies on 40 diabetic women who were at the menopausal or postmenopausal age. All patients treated were reported to have improved. Recently Mazer and his associates⁴⁶ reported 4 cases of diabetes in which stilbestrol was given for the treatment of menopausal symptoms. When 1 mg. of stilbestrol (equivalent to 50,000 international units of estrogen) was given hypodermically twice weekly, the insulin requirement was decreased materially, although the diet was not altered. The authors concluded, "There is, nevertheless, no advantage in the use of the estrogens, natural or synthetic, in the treatment of diabetes mellitus unless a severe menopausal syndrome coexists."

Observations such as those just mentioned are interesting but are far from conclusive. Such studies should be continued, but unwarranted conclusions should be avoided.

Acromegaly and Diabetes.—Coggeshall and Root⁴⁷ studied the coexistence of acromegaly and diabetes mellitus and analyzed 29 cases in which these two conditions were associated. The onset of acromegaly preceded that of diabetes mellitus by an average of nine and two-tenths years. They also reported a predisposition to diabetes in the families of diabetic patients who have acromegaly as compared with the families of patients who have acromegaly only. All these and similar clinical observations bear testimony to the interrelation of the glands of internal secretion, particularly with regard to the pituitary gland. We do not believe that knowledge at present has crystallized to the point where some of these comments may be accepted as facts; for example, we cannot agree with the observations and conclusions made by Hutton

45. Cantilo, E.: Successful Responses in Diabetes Mellitus of the Menopause Produced by the Antagonistic Action of the Hormones Toward Pituitary Activity, *Endocrinology* **26**:917-918 (May) 1940.

46. Mazer, C.; Israel, S. L., and Ravetz, E.: The Synthetic Estrogen, Stilbestrol: An Experimental and Clinical Evaluation, *J. A. M. A.* **116**:675-681 (Feb. 22) 1941.

47. Coggeshall, C., and Root, H. F.: Acromegaly and Diabetes Mellitus, *Endocrinology* **26**:1-25 (Jan.) 1940.

and his associates.⁴⁸ They stated that in many cases essential hypertension and diabetes mellitus resemble each other in so many respects as to suggest common etiologic factors, and they incriminated the pituitary, adrenal and thyroid glands. They reported the results of roentgen therapy over the adrenal and over the pituitary glands. We regard the evidence presented in this article as unconvincing and inconclusive.

Pancreatic Lesions and Diabetes.—Pancreatic lithiasis and diabetes still are reported as coexistent. Labbé⁴⁹ published an excellent review of this topic in 1938. Rockwern and Snively⁵⁰ reviewed the literature and reported the findings in 125 cases. Moolten⁵¹ reported a case of pancreatic lithiasis associated with diabetes and extensive necrotic pneumonia of mixed bacterial type.

Another condition of the pancreas with which diabetes occasionally coexists is acute pancreatitis. The association of these two diseases was reviewed recently by Shumacker.⁵² It is not surprising that diabetes develops among patients who have this acute pancreatic lesion, but it seems strange that it does not develop with greater frequency. Shumacker found that diabetes occurred in only 2 per cent of patients with severe pancreatitis and that of those patients who survived the acute illness, diabetes developed in 3 to 10 per cent.

Diabetes and Diabetes Insipidus.—Talbot and associates⁵³ reported another case of diabetes insipidus associated with diabetes mellitus.

Miscellaneous Acute Complications and Diabetic Coma.—Duncan and Jewesbury⁵⁴ discussed the management of acute complications of diabetes mellitus. They discussed the treatment of infection, degenerative change, gangrene, coronary occlusion, surgical conditions, ketosis and

48. Hutton, J. H.; Case, J. T.; Culpepper, W. L.; Olson, E. C., and Madden, E. E.: The Endocrine Aspect of Essential Hypertension and Diabetes Mellitus, *Endocrinology* **26**:418-426 (March) 1940.

49. Labbé, M.: Lithiase pancréatique et diabète, *Arch. d. mal. de l'app. digestif* **28**:913-934 (Nov.) 1938.

50. Rockwern, S. S., and Snively, D.: Pancreatic Lithiasis Associated with Pancreatic Insufficiency and Diabetes Mellitus: Report of Two Cases, *Arch. Int. Med.* **65**:873-881 (May) 1940.

51. Moolten, S. E.: Pulmonary Infection and Necrosis in Diabetes Mellitus: Report of a Case of Dissecting Necrotic Pneumonia Complicating Pancreatic Lithiasis, *Arch. Int. Med.* **66**:561-578 (Sept.) 1940.

52. Shumacker, H. B.: Acute Pancreatitis and Diabetes, *Ann. Surg.* **112**:177-200 (Aug.) 1940.

53. Talbot, J. H.; Coombs, F. S.; Consolazio, W. V., and Pecora, L. J.: Diabetes Insipidus Associated with Diabetes Mellitus: Metabolic Studies and Report of a Case, *Arch. Int. Med.* **66**:607-624 (Sept.) 1940.

54. Duncan, G. G., and Jewesbury, E. C. O.: The Management of the Acute Complications of Diabetes Mellitus, *M. Clin. North America* **23**:1533-1559 (Nov.) 1939.

pregnancy. In cases of mild infection they advised the administration of unmodified insulin if the level of fasting blood sugar exceeded 120 mg. per hundred cubic centimeters or if after meals the blood sugar exceeded 160 mg. In cases of moderately severe infection, they divided the usual dose of insulin into four equal doses. A specimen of the urine was examined before the administration of insulin; the patient was given a fourth of the total amount of food after the insulin had been administered. The amounts of insulin given were regulated by the results of urinalysis performed before administration. In cases of severe infection the authors advised that the total food and insulin be given in six equal doses. If the patient improved, the daily feedings were reduced to four and then to three, as before infection occurred. They felt that it was preferable to decrease the amount of insulin per dose rather than to omit a dose. They also commented that if infection of the urinary tract was present the dextrose in the urine may have been reduced by the organisms present, and the resultant absence or decrease may be misleading. In a discussion of surgical complications, the authors commented on their belief that a high content of blood fats predisposes to arteriosclerotic changes and gangrene, which concept had led them to reduce the amount of fat in the diet. In the discussion of gangrene, they gave as their indications for surgical intervention a rapid spreading of the gangrene, osteomyelitis, severe pain or advanced vascular disease. In regard to surgical operation, they advised the delay of anything except emergency intervention until the diabetes was under complete control. They agreed that spinal or local anesthesia, as well as that induced by nitrogen monoxide, is suitable, but they advised against the use of chloroform or ethyl chloride.

The treatment of diabetic coma employed by Duncan and Jewesbury is energetic. They advised the immediate administration of 100 units of protamine zinc insulin and 100 units of regular insulin subcutaneously and thereafter regular insulin every half-hour until the coma was controlled completely. They also utilized physiologic solution of sodium chloride and advised the use of sodium bicarbonate when the occasion demanded. Himsworth⁵⁵ again called attention to the fact that in cases of diabetic acidosis the abdominal symptoms may be sufficiently severe to suggest the presence of an intra-abdominal pathologic condition. He advised delay of operation until the ketosis was controlled. Duff and Williams⁵⁶ discussed the question of diabetes in operations on the urinary tract. Of 3,158 cases of disease of the urinary tract observed

55. Himsworth, H. P., in *Discussion on Surgery in Diabetic Patients*, Proc. Roy. Soc. Med. **32**:1002-1008, 1939.

56. Duff, J., and Williams, F. W.: *Diabetes in Surgical Urology*, J. Urol. **40**: 446-451 (Sept.) 1938.

over a period of five years, diabetes was present in 39; in 17 of them the patients were operated on, and the authors commented that with proper preoperative treatment they had found no greater operative risk than that in a comparable group of nondiabetic patients.

Diabetic Coma.—Owens and Rockwern⁵⁷ presented their observations in regard to the prognosis in cases of diabetic coma. They made the rather startling claim that the carbon dioxide level of the blood is not of prognostic importance. They felt, rather, that a more important basis for determining the eventual outcome is the patient's mental state. They feel that the mortality in coma depends primarily on the extent and previous duration of brain damage which is present when therapy is begun. The damage to the central nervous system seems to them unrelated to the severity of coexisting acidosis and pursues a course as yet unexplained.

Heck and Hall⁵⁸ remarked on the leukemoid reactions of the myeloid type which may be seen in cases of diabetic coma. The blood picture is similar to, or indistinguishable from, that seen in cases of leukemia. It is commonly associated with leukocytosis and a leukemoid reaction. Myeloid immaturity disappears promptly after institution of measures for the control of diabetes.

Vascular Disease.—Pearl and Kandel⁵⁹ studied the peripheral vascular system of 100 unselected diabetic patients. More than half of the patients complained of vascular symptoms; the majority of them disclosed abnormalities of the peripheral pulsation and other signs of peripheral vascular derangement. About 50 per cent of them had generalized arteriosclerosis. No relation was found between the degree of arteriosclerosis and the duration of the diabetes, but a direct relation was reported between the severity of the symptoms and the degree of peripheral vascular disease. Bowen, Regan and Koenig⁶⁰ offered proof that arteriosclerosis of the lower extremities can be prevented or delayed by continuous control of the diabetes, provided control is instituted early enough after inception of the diabetes. Root and his associates⁶¹

57. Owens, L. B., and Rockwern, S. S.: Prognosis in Diabetic Coma: Basic Importance of Mental State, *Am. J. M. Sc.* **198**:252-260 (Aug.) 1939.

58. Heck, F. J., and Hall, B. E.: Leukemoid Reactions of the Myeloid Type, *J. A. M. A.* **112**:95-101 (Jan. 14) 1939.

59. Pearl, F. L., and Kandel, A.: Peripheral Vascular Status of One Hundred Unselected Patients with Diabetes, *Arch. Surg.* **39**:86-96 (July) 1939.

60. Bowen, B. D.; Regan, J. S., and Koenig, E. C.: The Development of Arteriosclerosis in the Diabetic, Based on the Study of a Group of Patients During Ten to Thirteen Years, *Ann. Int. Med.* **12**:1996-2005 (June) 1939.

61. Root, H. F.; Bland, E. F.; Gordon, W. H., and White, P. D.: Coronary Atherosclerosis in Diabetes Mellitus: A Postmortem Study, *J. A. M. A.* **113**:27-30 (July 1) 1939.

studied the question of coronary atherosclerosis associated with diabetes mellitus. The study was made post mortem and consisted in a comparison of atherosclerotic lesions in the coronary arteries of 349 diabetic patients and 3,400 nondiabetic patients. They found that the incidence of coronary occlusion was much more frequent in the diabetic than in the nondiabetic group. For example, of the patients between the ages of 40 and 60, 23 per cent of those who had diabetes had coronary occlusion, as compared with 6 per cent of the nondiabetic group. Coronary sclerosis without occlusion also was found more commonly in the diabetic group. There was no significant atherosclerosis with occlusion or narrowing in 49 per cent of the diabetic group or in 82 per cent of the nondiabetic group. They found that occlusion of a coronary artery occurred among diabetic women almost as frequently as among diabetic men, whereas in the nondiabetic patients under 60 years of age it was far less frequent among women than among men.

Williams and O'Kane⁶² suggested a clinical classification of lesions of the lower extremities associated with diabetes. They separated vascular involvement from infectious involvement. Murray⁶³ also discussed the question of diabetic infection and gangrene. He suggested that increasing attention should be given to minor infectious lesions. He also advised local amputation in a few cases of localized gangrene, but emphasized that radical amputation is required in cases of fulminating infection or extensive gangrene.

Diabetes and Ocular Conditions and Neuritis.—Smith⁶⁴ listed the diabetic manifestations seen in cases of ophthalmic disease. He commented on the rarity of lipaemia retinalis and pointed out that Moore of London reported he had not seen a case of this condition since insulin was introduced. Retrobulbar neuritis occasionally is seen among older persons. It produces a typical small central scotoma and usually responds to treatment. This condition, if allowed to progress, may result in atrophy. He felt that iritis may be due to lowered resistance to infection. The cataracts are mostly of the senile type, which develop earlier among diabetic patients than among nondiabetic patients. A true diabetic cataract in a young person occurs bilaterally and develops rapidly.

Smith found, too, that diabetic retinitis usually is associated with hypertension, vascular disease and albuminuria. It may be difficult

62. Williams, F. W., and O'Kane, T. J.: Clinical Classification of Lesions of the Lower Extremities Associated with Diabetes: A Guide for Operation and the Level of Amputation, *Arch. Surg.* **40**:685-693 (April) 1940.

63. Murray, G.: Diabetic Infection and Gangrene, *Canad. M. A. J.* **41**:246-250 (Sept.) 1939.

64. Smith, W. J.: Diabetic Manifestations in Ophthalmology, *Southwestern Med.* **23**:14-15 (Jan.) 1939.

to decide the cause of retinitis. He stated that hemorrhage at the time of operation on the eye occurs more frequently among diabetic than among nondiabetic patients. Refractive errors are common. Some undoubtedly are due to an alteration of osmotic pressure in the aqueous humor with altered index of refraction in the lens cortex. This change is commonly seen shortly after treatment with insulin is instituted. Recent literature does not disclose anything hopeful in the treatment of diabetic retinitis. The so-called antihemorrhagic vitamins, such as vitamins C and K, are being given a trial and snake venom is also being used because of its antihemorrhagic effect. It is to be hoped that within a few years the effect of the latter agent may be evaluated properly. Another discouraging complication of diabetes is diabetic neuritis. Wohl⁶⁵ stated that diabetic neuritis is associated with a lack of vitamin B.

Vitamin Deficiency and Metabolism of Carbohydrate.—Sydenstricker and his associates⁶⁶ reported 2 cases in which complications of diabetes occurred; clinical signs of pellagra developed when the carbohydrate content of the diet was increased and an increased amount of insulin was given. In both cases the patients responded to vitamin therapy. The authors expressed the opinion that the rapid metabolism of carbohydrates secured among diabetic patients treated with insulin is accompanied by the correspondingly rapid depletion of the coenzymes; in this way signs of avitaminosis may be produced. Other explanations, such as inadequate absorption or storage of vitamins and coenzymes, were considered. Rudy⁶⁷ also reported a case in which diabetes was associated with a vitamin deficiency disease.

Owens and his associates⁶⁸ evaluated vitamin B therapy for diabetic patients. They expressed the opinion that the usual diabetic diets contain adequate amounts of thiamine and riboflavin in relation to their total caloric value. They did not find that the administration of large amounts of thiamine hydrochloride and riboflavin for many weeks to patients with well controlled diabetes had any effect on the requirement of insulin or that it altered the severity of the diabetes. They concluded that diabetic patients did not need vitamin therapy when the diabetes was well controlled. They did feel, however, that thiamine hydrochloride

65. Wohl, M. G.: Neuritis of Diabetes Mellitus and Avitaminosis B, J. A. M. A. **113**:164 (July 8) 1939.

66. Sydenstricker, V. P.; Geeslin, L. E., and Weaver, J. W.: Avitaminosis Occurring in Diabetic Patients Under Insulin Therapy, J. A. M. A. **113**:2137-2138 (Dec. 9) 1939.

67. Rudy, A.: An Unusual Case of Deficiency Disease in a Patient with Diabetes Mellitus, Endocrinology **27**:206-211 (Aug.) 1940.

68. Owens, L. B.; Rockwern, S. S., and Brown, E. G.: Evaluation of Vitamin B Therapy for Diabetes, Arch. Int. Med. **66**:679-687 (Sept.) 1940.

has a beneficial effect on patients suffering from diabetic neuritis. Kaufman⁶⁹ reviewed the influence of thiamine on the level of blood sugar in diabetic patients. He found absolutely no effect from the use of this vitamin in the treatment of patients with uncomplicated diabetes. Brazer and Curtis⁷⁰ discussed vitamin A deficiency in diabetes mellitus. They studied a group of 20 patients who had juvenile diabetes; all were found to have poor adaptation to light. Three of the group were subjectively aware of night blindness, and 9 of them disclosed cutaneous changes compatible with deficiency of vitamin A. The daily administration of 60,000 units of crystalline carotene dissolved in vegetable oil for as long as fourteen days did not affect the adaptation to light of patients who had diabetes mellitus. However, when 60,000 units of vitamin A were administered daily to patients in the form of concentrated fish liver oils, their adaptation to light returned to normal or near normal in periods ranging from three to twenty-one days. The authors expressed the belief that the cause of poor adaptation to light in cases of juvenile diabetes appeared to be due to an inability to convert carotene into vitamin A.

Dye and Chidsey⁷¹ studied the utilization ratio for ketone bodies and total carbohydrate and its relation to the problem of ketosis. They used 9 normal, 7 eviscerated and 10 depancreatized dogs. In addition to studying the problem of ketosis, they also confirmed the observations of Soskin and Levine that the consumption of carbohydrate by a diabetic dog at its characteristic blood sugar level may be as high or even higher than that of a normal animal at its characteristic blood sugar level. They concluded that by the exclusion of an extrahepatic origin of ketosis and seat of "antiketosis" the present evidence supported the "overproduction" theory. According to this theory, the primary, if not the only, site of production of ketone bodies is the liver, and the antiketogenic action of insulin, dextrose and other glycogen formers is one of inhibiting the production of these bodies by this organ, possibly through a mechanism which involves the anterior lobe of the pituitary gland.

Diet.—Limited space prevents detailed consideration of the various types of diet now used in the treatment of diabetes mellitus. Suffice it to say that there is as yet no conclusive evidence that any one type of diet is suitable for every physician to prescribe. Some continue to

69. Kaufman, R. E.: Influence of Thiamine on Blood Sugar Levels in Diabetic Patients, *Arch. Int. Med.* **66**:1079-1086 (Nov.) 1940.

70. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, *Arch. Int. Med.* **65**:90-105 (Jan.) 1940.

71. Dye, J. A., and Chidsey, J. L.: Ketone Body-Total Carbohydrate Utilization Ratios and Their Relation to the Problem of Ketosis, *Am. J. Physiol.* **127**: 745-750 (Nov.) 1939.

believe that the diet should be high in carbohydrate and low in fat; this opinion is based on the incidence of arteriosclerosis in cases of diabetes mellitus. The evidence for this statement is as yet not approved generally. It can be said that the majority of internists interested in the treatment of diabetes mellitus now are prescribing diets which are higher in carbohydrate and lower in fat than those which were used previously.

Richardson ⁷² presented a simplified method for calculation of diabetic diets and listed seven diets in order to simplify the figuring. In these diets, all portions were given, with the exception of the amount of butter and bread necessary to make up the caloric needs. The physician need only know the amount of protein desired in order to find a suitable diet for a patient. This method is similar to that which has been employed for many years at the Mayo Clinic. Lovell and Rabinowitch ⁷³ discussed the factors influencing the storage of protein with low caloric diets. Studies were made of the nitrogen metabolism of diabetic patients treated with various low caloric diets which contained different amounts of carbohydrate and fat and different amounts of vegetable and animal protein. They expressed the opinion that the carbohydrate tends to enhance, whereas the fat tends to interfere with, the storage of protein in the body. The latter is influenced not only by the total amount of protein in the diet but by the relative amount of protein of high biologic (protein-sparing) value.

INSULIN

Mainzer ⁷⁴ studied the hypersensitivity to insulin of patients who have pellagra. He commented on some of the points which pellagra and Addison's disease have in common and noted that anatomic lesions of the adrenal cortex may be found in many cases of pellagra. The author studied the blood sugar curve in 16 of 21 cases of pellagra after subcutaneous injection of 5 units of unmodified insulin. He found that the resultant decreased values for blood sugar were marked and persisted for more than five hours. The subsequent elevation of the level of blood sugar was retarded or absent. In several cases this small dose of insulin produced severe hypoglycemic shock. The abnormal reaction persisted even after clinical improvement or cure of the pellagra, and consequently the author suggested that it was not due to a deficiency of the vitamin B complex. Mainzer expressed the belief that neither the liver nor the

72. Richardson, R.: A Simplified Method for Calculating Diabetic Diets, *Am. J. M. Sc.* **199**:102-108 (Jan.) 1940.

73. Lovell, M. E., and Rabinowitch, I. M.: Factors Influencing Storage of Protein with Low-Calorie Diets, *J. Nutrition* **18**:339-351 (Oct.) 1939.

74. Mainzer, F.: Ueber Pellagra: II. Insulin—Ueberempfindlichkeit bei Pellagrakranken, *Acta med. Scandinav.* **100**:208-243 (June 14) 1939; abstracted, *J. A. M. A.* **113**:986 (Sept. 2) 1939.

anterior lobe of the pituitary gland could be considered responsible for this exaggerated response to insulin, but that it could be related to a functional failure of the adrenal glands of patients who have pellagra.

Ralli and Sherry ⁷⁵ studied the effect of insulin on the plasma level and urinary excretion of vitamin C of pancreatectomized dogs. They found that the plasma level and the urinary excretion of vitamin C decreased markedly as soon as a subcutaneous dose of insulin became effective. If dextrose was administered intravenously at the same time that the plasma level and the urinary excretion of vitamin C were observed to be reduced, the effect of the insulin could be overcome and the plasma level of vitamin C returned to normal. Burke and McIntyre ⁷⁶ studied the effect of nicotinic acid and the vitamin B complex on the tolerance of rats to insulin. Various fractions of the vitamin B complex produced varying results. The authors concluded that nicotinic acid was at least partially responsible for the antagonistic action of the heat-stable portion of the vitamin B complex to the hypoglycemic effect of insulin.

Gemmill ⁷⁷ studied the effect of insulin on the glycogen content of isolated muscles and measured it by determining the glycogen content of different isolated muscles after they had been suspended for some time in Ringer's solution containing dextrose and with or without the addition of unmodified insulin. The glycogenic content of the sartorius muscles of frogs did not change in the presence of insulin; however, the diaphragmatic muscle of rats disclosed an appreciable increase in glycogen when insulin was present. When the amount of glycogen present in rats' diaphragms which had been suspended in the solution to which insulin had been added was compared with the content of glycogen present prior to that procedure, it was found that a definite synthesis of glycogen had taken place. If the surrounding medium did not contain dextrose, or if ovalbumin or small amounts of inactivated insulin were substituted for the active insulin, the content of glycogen in the muscle did not increase. The insulin did not increase the oxygen uptake of a rat's diaphragm. The author concluded that insulin aids in the conversion of dextrose to glycogen in isolated muscle.

Types of Insulin.—Recently many articles have been written in regard to the best type of insulin for general use, the best time of day for its administration and a number of other related problems. It is

75. Ralli, E. P., and Sherry, S.: Effect of Insulin on Plasma Level and Excretion of Vitamin C, *Proc. Soc. Exper. Biol. & Med.* **43**:669-672 (April) 1940.

76. Burke, J. C., and McIntyre, A. R.: Nicotinic Acid and the Vitamin B Complex in Insulin Tolerance, *J. Pharmacol. & Exper. Therap.* **67**:142-146 (Oct.) 1939.

77. Gemmill, C. L.: The Effect of Insulin on the Glycogen Content of Isolated Muscles, *Bull. Johns Hopkins Hosp.* **66**:232-244 (April) 1940.

impossible to review all of these articles or to review any of them in detail. A few, however, have been included in one footnote.⁷⁸ In summary, it may be said that there is a unanimity of opinion that protamine zinc insulin has a definite role in the treatment of diabetes mellitus. There is not such agreement, however, in regard to the other types of insulin. There is little evidence that crystalline insulin, by whatever name it is known, has a much different effect from the unmodified type of insulin used in past years. By now, each physician has had an opportunity to determine whether he obtains the best results from the administration of protamine zinc insulin in the morning or at night, whether it is better to administer the protamine and the regular insulin in separate syringes and at separate sites or in the same syringe and whether great attention must be paid to the amount of glycosuria or to the level of blood sugar. All these and many other problems will undoubtedly remain controversial for a number of years.

Subcutaneous implantation of tablets of insulin is also being studied. Recent reports do not suggest that this method is yet ready for general clinical application.⁷⁹ If it were possible to implant subcutaneously the correct amount of insulin needed to control the diabetes for a long period, treatment of the disease would have made a definite advance. The most obvious disadvantage is that after implantation there is no way in which allowance may be made for any change in the patient's requirement for insulin. Regardless of the amount of his physical activity, the state of his health or the amount of food ingested, the implanted insulin would be absorbed at the same rate.

78. Martin, H.; Drury, D. R., and Strouse, S.: Basal Insulin Requirement in Diabetes Mellitus, *Arch. Int. Med.* **66**:78-92 (July) 1940. Mark, M. F.: Optimum Time for Administration of Protamine Zinc Insulin, *ibid.* **64**:897-906 (Nov.) 1939. Ricketts, H. T., and Wilder, R. M.: Solutions of Amorphous Insulin and Solutions of Zinc Insulin Crystals: Clinical Studies on the Comparative Speed and Duration of Action, *J. A. M. A.* **113**:1310-1312 (Sept. 30) 1939. Duncan, G. G.; Cuttle, T. D., and Jewesbury, E. C. O.: Observations on the Comparative Clinical Values of Zinc Insulin Crystals in Solution and Unmodified Insulin, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* **3**:293-306 (Dec.) 1939. Allen, F. M.: Comparison of Different Preparations of Amorphous and Zinc Crystalline Insulin, *Endocrinology* **26**:208-217 (Feb.) 1940. Jackson, R. L.; Boyd, J. D., and Smith, T.: Interchangeability of Zinc Crystalline Insulin and Amorphous Insulin, *Am. J. Dis. Child.* **59**:1050-1053 (May) 1940. Hechter, O.; Levine, R., and Soskin, S.: Possible Physiologic Significance of the Zinc Content of Insulin, *Proc. Soc. Exper. Biol. & Med.* **43**:361-363 (Feb.) 1940. Morris, N.: The Newer Insulins, *Glasgow M. J.* **133**:1-19 (Jan.) 1940.

79. Mark, J., and Biskind, G. R.: The Increased Duration of Insulin Action by the Use of Protamine Zinc Insulin in Pellet Form, *Endocrinology* **26**:444-448 (March) 1940. Parkes, A. S., and Young, F. G.: The Influence of the Subcutaneous Implantation of Tablets of Solid Insulin on the Blood Sugar Level of the Rabbit, *J. Endocrinol.* **1**:108-116 (June) 1939.

Globin insulin is a combination of insulin and beef globin. Recent reports indicated that it is certainly worthy of further clinical trial.⁸⁰ Marks pointed out that this type of insulin is not as soluble in serum as is protamine zinc insulin and that globin does not interact with the serum proteins but simply combines with the insulin. He reported that it has a more rapid effect during the first two or three hours after injection than does protamine zinc insulin. The prolonged hypoglycemic effect thereafter is about equal in intensity to that of protamine zinc insulin, but is shorter in duration, ending within twenty-four hours. Therefore, although it takes care of the meals eaten during the course of the day, it does not necessitate bedtime feedings in order to prevent hypoglycemia during the night.

Many physicians have been hoping for a type of insulin which would require only one injection and which would have not only a prompt effect that would take care of the ingested food but a prolonged stabilizing effect. As will doubtless be recalled, it was at first thought that the ideal type of insulin had at last been discovered in protamine zinc insulin. There are still those, notably Tolstoi and his associates, who prefer to use a single dose of protamine zinc insulin, even though it may not control the glycosuria or the hyperglycemia. In July 1939 they⁸¹ reported their results of the treatment of 2 patients who had severe diabetes and who were given a constant diet, consisting of 200 Gm. of carbohydrate, 75 Gm. of protein and 60 Gm. of fat, and a constant dose of 50 units of protamine zinc insulin every morning before breakfast over a period of strict observation in the metabolic ward. Despite the fact that each patient had constant hyperglycemia and glycosuria, excreting as much as 150 Gm. of dextrose in twenty-four hours, neither had polyuria or polydipsia, neither lost weight and neither showed a change in nitrogen equilibrium during the period of observation. Subsequently, these same authors⁸² reported on a series of 84 ambulatory

80. Bauman, L.: Clinical Experience with Globin Insulin, *Am. J. M. Sc.* **198**: 475-481 (Oct.) 1939. Reiner, L.; Searle, D. S., and Lang, E. H.: On the Hypoglycemic Activity of Globin Insulin, *J. Pharmacol. & Exper. Therap.* **67**:330-340 (Nov.) 1939. Marks, H. E.: A New Globin Insulin: The Importance of Carbohydrate Distribution in the Control of Diabetes with the Modified Insulins, *M. Clin. North America* **24**:649-670 (May) 1940. Andrews, G. B.; Groat, W. A.; Wood, A. V., and Jones, M. L.: Globin Insulin: A Clinical Study, *New York State J. Med.* **40**:913-917 (June 15) 1940.

81. Tolstoi, E., and Weber, F. C.: Protamine Zinc Insulin: A Metabolic Study; Treatment in Two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, *Arch. Int. Med.* **64**:91-104 (July) 1939.

82. Tolstoi, E., and Weber, F. C.: Protamine Zinc Insulin: A Clinical Study; Report of a Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year, *Arch. Int. Med.* **66**:670-678 (Sept.) 1940.

patients similarly treated for a year or more. These patients also were given estimated diets which contained 200 to 250 Gm. of carbohydrate and a single dose of protamine zinc insulin each morning. Twenty-seven patients out of this group had such severe diabetes that glycosuria was present constantly; no effort was made to obtain sugar-free urine by altering the diet or the dose of insulin. However, if ketonuria was present or if the patient lost weight, the amount of protamine zinc insulin was increased until the ketonuria disappeared and a gain in weight was noted. Severe ketonuria was specifically treated by oral administration of sodium chloride plus frequent doses of unmodified insulin. Among these 27 patients, 19 gained weight, 6 lost weight and 2 maintained the same weight; none of them had polyuria or polydipsia; none showed any increased incidence of infection, and all maintained a normal nitrogen balance.

Tolstoi suggested that for patients who are being treated with protamine zinc insulin the therapy may be considered as adequate when there are maintenance of body weight, freedom from symptoms of diabetes and absence of ketonuria. He stated that he "was not concerned about the hyperglycemia or the amount of dextrose excreted."

Much controversy has been aroused by these reports. Joslin and his associates⁸³ challenged Tolstoi's statement that patients can excrete as much as 150 Gm. of dextrose in twenty-four hours and still maintain their weight and their state of nitrogen equilibrium over a prolonged period. They further pointed out that it is "unlikely" that these patients can remain free of polyuria or polydipsia while they are excreting in the urine 5 to 10 per cent of sugar. They condemned Tolstoi's practice of allowing patients who have definite acidosis to carry out their own treatment at home and stated that forty-two years of experience with diabetes in their own clinic had shown them that methods designed to control hyperglycemia and glycosuria result in a reduced incidence of coma and other complications of diabetes and an increase in the length of life of the average diabetic patient.

Tolstoi⁸⁴ shortly thereafter replied that he had simply presented the facts as he had observed them. He added that with the use of protamine zinc insulin, the criteria of good diabetic control must be revamped, since "by the use of this hormone, carbohydrate oxidation is assured for about a twenty-four hour period."

Allen⁸⁵ sided with Joslin and his associates in this argument. He reported 2 cases in which disregard of the dietary and insulin control of diabetes over a period of several years greatly increased the require-

83. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes, *J. A. M. A.* **115**:1038-1039 (Sept. 21) 1940.

84. Tolstoi, E.: Treatment of Diabetes, *J. A. M. A.* **115**:1296 (Oct. 12) 1940.

85. Allen, F. M.: Diabetes, *J. A. M. A.* **115**:1474-1475 (Oct. 26) 1940.

ments of insulin. He concluded that "diabetic patients treated just sufficiently to keep them out of acute trouble for a few years constitute the reservoir from which are drawn the great mass of complications which cause most diabetic deaths today."

It will be many years before Tolstoi and his associates will have the opportunity of properly evaluating their observations, since it will require a long period to determine the incidence of such complications as diabetic retinitis and neuritis among patients treated according to their methods. In the meantime, it will undoubtedly be preferable to leave the study of such methods of treating diabetes to well organized groups like Tolstoi's rather than to introduce such revolutionary concepts into the care of diabetic patients by the average physician.

More recently, various other types of insulin have been reported which provide the type of control of diabetes that every one is seeking. In several reports the use of hexamine insulin (a compound of insulin and hexamethylene tetramine) was advocated.⁸⁶ Alpert^{86a} reported the cases of 2 boys, one 9 and the other 16 years of age, who received single injections of a mixture of protamine zinc insulin and hexamine insulin before breakfast, with good results. He expressed the opinion that, although mixed, the two insulins retained their individual characteristics, the hexamine insulin producing an immediate and intermediate action and the protamine zinc insulin a delayed action. Feinblatt and his associates^{86b} reported that a single dose of the hexamethylene tetramine-insulin compound gave both a rapid and a sustained action. They reported that a single dose of this new insulin produced a blood sugar curve similar to the one produced by four divided doses of standard insulin, but with decided constriction in the range of fluctuations of the levels of blood sugar. The hypoglycemic shock experienced with this preparation was comparable to that which may follow the use of regular insulin and responded promptly to the ingestion of carbohydrates.

Insulin Shock Therapy.—Tremendous doses of insulin have been utilized extensively within the last few years for the induction of shock in the treatment of various conditions. Jourdonais and Bruger⁸⁷ studied the sojourn of insulin in the blood of rabbits after the administration of

86. (a) Alpert, B.: Juvenile Diabetes Mellitus Treated with Protamine-Hexamine Insulin—a New Combination: Clinical Case Reports, *Arch. Pediat.* **56**:647-649 (Oct.) 1939. (b) Feinblatt, H. M.; Ferguson, E. A., and Alpert, B.: Hexamine Insulin: Juvenile Type of Diabetes Treated with Hexamethylene Tetramine Insulin Compound Giving Rapid and Sustained Action, *Endocrinology* **26**:437-443 (March) 1940.

87. Jourdonais, L. F., and Bruger, M.: The Sojourn of Insulin in the Blood of Rabbits After the Administration of Massive Doses of Insulin, *Endocrinology* **26**:250-254 (Feb.) 1940.

massive doses of insulin. They injected 1,000 units of insulin into rabbits and studied the amount of insulin in the blood stream for sixty to ninety minutes after injection. More than ninety minutes after injection, insulin could not be recovered from the blood by the procedure which they employed, although the effect of the insulin, as measured by the hypoglycemia, persisted for as long as nine hours. It is interesting to note that in 2 animals this massive dose of insulin was followed by a gradual and persistent rise of the level of blood sugar; the usual hypoglycemic effect of insulin was not evident. In spite of extremely high levels of the blood sugar, these animals died in convulsive seizures not unlike those seen in insulin shock. Five rabbits in this series showed only transient hypoglycemia, lasting approximately an hour. The authors stated that massive doses of insulin may so disturb the carbohydrate metabolism as to result in ketosis.

Appel and Hughes⁸⁸ studied schizophrenic patients who were receiving tremendous doses of insulin for shock therapy. They found that if insulin was given for as long as two months in daily doses large enough to produce coma in patients whose carbohydrate metabolism was normal, an elevation of the dextrose tolerance curves would also be produced. This effect disappeared in two to three months after cessation of therapy. Kaplan and Low⁸⁹ studied both dextrose and insulin tolerance tests in relation to insulin shock treatment. Although the average blood sugar curve of 26 patients who had received such treatment and who were subsequently given a dextrose tolerance test was within normal limits, in only 6 cases were the individual curves normal. The blood sugar curves obtained in the insulin tolerance tests of these 26 patients were characterized by a marked prolongation of the time required for a return to the fasting level of blood sugar. There was no correlation between the results of the insulin therapy and the dextrose tolerance tests and the average dose required to produce coma. The onset of coma seemed dependent not only on a significant decrease in the level of blood sugar but on the length of time the low level was maintained.

Sherrill and MacKay⁹⁰ studied the effects of tremendous doses of insulin on the rat. They reported that the administration of dextrose was without influence if the duration of the convulsion was long. Insulin-treated rats died of respiratory failure and at necropsy were

88. Appel, J. W., and Hughes, J.: The Effect of Large Doses of Insulin on Glucose Tolerance, *Am. J. M. Sc.* **199**:829-833 (June) 1940.

89. Kaplan, M., and Low, A. A.: Glucose and Insulin Tolerance: Relation to Insulin Shock Treatment, *Am. J. Psychiat.* **96**:689-697 (Nov.) 1939.

90. Sherrill, J. W., and MacKay, E. M.: Deleterious Effects of Experimental Protamine Insulin Shock, *Arch. Int. Med.* **64**:907-912 (Nov.) 1939.

found to have definite edema of the lungs. Administration of strong solutions of dextrose by stomach tube or intraperitoneally to rats that had been in insulin shock for some time was often followed by convulsions and death. Occasionally, water had the same effect. These results were due to the sudden shift in electrolytes and changes in the concentration of body fluids superimposed on an impaired general circulation and cerebral stasis and to degenerative changes, especially in the brain, caused by hypoglycemia. They felt that prolonged hypoglycemia caused permanent functional damage to the brain. After five or six days they noted sensory and motor disturbances, such as impaired vision and hearing, incoordination, spasticity and paralysis.

Results of such studies on rats may explain some of the unfortunate conditions which have been seen among diabetic patients after severe reactions to insulin. Frostig⁹¹ reported clinical observations of 6,587 treatments of schizophrenia with insulin. He found that at first the cerebral cortex became suppressed and released the syndromes associated with activity of the basal ganglions. Activity of the basal ganglions later ceased and gave way to release of the midbrain. Finally, centers in the medulla were released. If signs of medullary release lasted beyond the time at which pinpoint pupils were observed and the corneal reflex disappeared, protracted shock resulted. This point was considered by the author to be the biologic borderline, beyond which treatment could not be continued safely. Sonenthal and Low⁹² studied the electrographic tracings of patients after combined shock therapy with insulin and metrazol. They found no evidence of myocardial damage in 36 cases studied after termination of the entire course of treatment with both metrazol and insulin.

Miscellaneous.—The question as to whether antibodies may develop after the use of insulin has been discussed for some time. Wasserman and his associates⁹³ studied the antigenic property of insulin. They stated that insulin could be considered antigenic because serums from insulin-sensitized rabbits may give a positive reaction in the complement fixation test. Sufficient foreign protein evidently was present in commercially prepared insulin to allow sensitization of a rabbit to that protein by repeated injection of the insulin. Antibodies produced against insulin were not found to act as antihormones. Marble and his

91. Frostig, J. P.: Clinical Observations in the Insulin Treatment of Schizophrenia: Preliminary Report; I. The Symptomatology and Therapeutic Factors in the Insulin Effect, *Am. J. Psychiat.* **96**:1167-1190 (March) 1940.

92. Sonenthal, I. R., and Low, A. A.: Electrocardiographic Studies After Treatment with Insulin and Metrazol Shock, *J. Nerv. & Ment. Dis.* **91**:423-427 (April) 1940.

93. Wasserman, P.; Broh-Kahn, R. H., and Mirsky, I. A.: The Antigenic Property of Insulin, *J. Immunol.* **38**:213-219 (March) 1940.

co-workers⁹⁴ studied the effect of plasma from diabetic patients on the blood sugar curves of rabbits following the injection of insulin. Their method was similar to that described by Dohan.⁹⁵ They reported the effect of a single subcutaneous injection of approximately 10 cc. of blood plasma from diabetic patients on the hypoglycemic effect of insulin on rabbits. With two exceptions, no significant alterations in the rabbits' blood sugar curves were found even when plasma from obese middle-aged or elderly women who had mild diabetes was used. The series of patients from whom samples of blood plasma were obtained also included 5 who had high requirements for insulin. When the plasma of 2 of these 5 patients was used, a definite lessening of the hypoglycemic effect of insulin subsequently injected into the rabbits was present and persisted for three to five weeks. The results could not be duplicated, however, with serum collected from the same 2 patients at a later date.

HYPERINSULINISM

During 1940 there were two advances in our knowledge of hyperinsulinism. The first was the report of additional proved cases of this interesting condition; the second was the increasing insistence that the term hyperinsulinism be reserved for those cases in which there is proof that the symptoms are caused by the excessive production of endogenous insulin.

True hyperinsulinism is a rare disease. Frantz,⁹⁶ who recently reviewed the world literature, found only 96 cases in which the diagnosis had been proved at operation or necropsy. Hypoglycemia, on the other hand, is much more common and may be present physiologically or may be due to any one of many disturbances in carbohydrate metabolism. Meakins⁹⁷ reported 3 cases of postencephalitic Parkinson's disease in which attacks of convulsions were associated with low values of blood sugar. He urged further search for other cases in which a connection between a hypothalamic lesion and hypoglycemia was suggested. Adlersberg and Friedman,⁹⁸ who reported on disturbances of carbohydrate metabolism in 21 cases of postencephalitic Parkinson's disease, observed pathologically low levels of blood sugar in only 3 cases; these

94. Marble, A.; Fernald, A. T., and Smith, R. M.: Effect of Human Diabetic Plasma upon Blood Sugar Curves in Rabbits Following Insulin, *Endocrinology* **26**:735-742 (May) 1940.

95. Dohan, F. C.: Analysis of Insulin Response of Rabbits After Injection of Diabetic Serum, *Proc. Soc. Exper. Biol. & Med.* **39**:24-28 (Oct.) 1938.

96. Frantz, V. K.: Tumors of Islet Cells with Hyperinsulinism: Benign, Malignant and Questionable, *Ann. Surg.* **112**:161-176 (Aug.) 1940.

97. Meakins, J. C.: Hypoglycemia Following Encephalitis, *Ann. Int. Med.* **13**: 1830-1836 (April) 1940.

98. Adlersberg, D., and Friedman, R., cited by Meakins.⁹⁷

levels were observed after oral administration of 50 Gm. of dextrose. Hypoglycemia was reported by Rathery, Dérot and Sterne⁹⁹ in 2 cases of subdural hemorrhage and by Birnbaum and Wood¹⁰⁰ in cases of dementia paralytica.

Hyperglycemia may be present in many instances without associated organic disease. Matthews¹⁰¹ determined the postabsorptive values of blood sugar of 117 normal persons and found that they varied from 0.06 to 0.11 Gm. per hundred cubic centimeters of whole blood; the values of 70 per cent fell between 0.07 and 0.08 Gm. Hart and Lisa¹⁰² analyzed all determinations of blood sugar, including routine determinations in 21,000 cases, made over a six year period at the New York City Hospital. In about 11 per cent of cases the concentration of blood sugar was less than 0.08 Gm. per hundred cubic centimeters of whole blood, in 7 per cent between 0.070 and 0.079 Gm., in 2.3 per cent between 0.060 and 0.069 Gm., in 0.8 per cent between 0.050 and 0.059 Gm. and in 0.4 per cent less than 0.050 Gm. Symptoms were not noted in any case, with the exception of 1 in which the level of blood sugar was 0.030 Gm. per hundred cubic centimeters.

Sufficiently strenuous exercise may produce severe hypoglycemia even among trained and healthy athletes.¹⁰³ Patients who are nervous or high-strung seem less able than others to withstand effectively the strain placed on the homeostasis of the blood sugar by exercise. Michael¹⁰⁴ performed several determinations of the blood sugar on each of 30 golfers while they were playing eighteen holes of golf after eating their usual luncheon. The values dropped to hypoglycemic levels (the average value was 0.054 Gm. per hundred cubic centimeters) between the ninth and fifteenth holes, or about two hours after the meal. The

99. Rathery, F.; Dérot, M., and Sterne, J.: Hypoglycémie dans deux cas d'hémorragie méningée sous-arachnoïdienne, *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:1578-1582 (Nov. 2) 1931.

100. Birnbaum, L., and Wood, J. A.: Hypoglycemia as a Cause of Seizures in General Paralysis, *M. Bull. Vet. Admin.* **14**:236-240 (Jan.) 1938.

101. Matthews, M. W.: A Study of the One Dose Three Hour (Standard) and the Two Dose One Hour (Exton-Rose) Glucose Tolerance Tests, Thesis, University of Minnesota Graduate School, 1939.

102. Hart, J. F., and Lisa, J. R.: The Rate of Occurrence of Hypoglycemia: Study of Twenty-One Thousand Routine Fasting Blood Sugars, *Endocrinology* **27**:19-22 (July) 1940.

103. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, with Especial Reference to the Development of Hypoglycemia, *J. A. M. A.* **82**:1778-1779 (May 31) 1924. Jokl, E.: Sportärztliche Kasuistik, *Klin. Wchnschr.* **12**:913-914 (June 10) 1933.

104. Michael, P.: Blood Sugar Studies on Golfers, *J. A. M. A.* **115**:286-287 (July 27) 1940.

hypoglycemic period corresponded to a period of fatigue, mild symptoms of hypoglycemia and lessened efficiency, as reflected by poorer scores. Both the hypoglycemia and the severity of symptoms were exaggerated among the poorer golfers, apparently because of tension, anxiety and greater output of energy, and were far less than average among the expert golfers, who were usually well poised and relaxed. A second observation was made on the same golfers after they had eaten food which contained more fat and less carbohydrate; consumption of sugar or candy at the seventh and eighth holes resulted in elimination of both hypoglycemia and its symptoms and achievement of much better scores.

THE PITUITARY GLAND

Some of the literature pertaining to the pituitary gland has been reviewed by one of us (E. H. R.) and Schweiger.¹⁰⁵ Reference will be made again to some of that material, as well as to other articles which deal with the relation of the pituitary gland to certain phases of metabolism. The relation of the gland to metabolism of carbohydrates will be considered first. Marks and Young¹⁰⁶ have published many articles in this field, a few of which will be mentioned.

Young¹⁰⁷ reviewed his concept of the relation of the pituitary gland to metabolism of carbohydrates. He began with Houssay's observations, in 1924, (1) that hypophysectomy increased the sensitivity to insulin in normal animals and decreased the intensity of the diabetes in depancreatized animals, (2) that administration of preparations of the anterior lobe of the pituitary gland to normal or hypophysectomized animals decreased their sensitivity to the hypoglycemic effect of insulin, (3) that administration of similar preparations to hypophysectomized depancreatized animals increased the severity of the diabetes and (4) that administration of suitable anterior pituitary extract to normal animals can induce diabetes. Young also reviewed some of the actions of the extract of the anterior lobe of the pituitary. He discussed the anti-insulin action which causes insensitivity to the subsequent injection of insulin. The so-called glycotropic principle may not itself be

105. Ryneerson, E. H., and Schweiger, L. R.: Review of Literature on the Pituitary Body (1938 and 1939), *Arch. Int. Med.* **66**:226-290 (July) 1940.

106. Marks, H. P., and Young, F. G.: The Hypophysis and Pancreatic Insulin, *Lancet* **1**:493-497 (March 16) 1940; Observations on the Metabolism of Dogs Made Permanently Diabetic by Treatment with Anterior Pituitary Extract, *J. Endocrinol.* **1**:470-510 (Dec.) 1939. Young, F. G.: The Relation of the Anterior Pituitary Gland to Carbohydrate Metabolism, *Brit. M. J.* **2**:393-396 (Aug. 19) 1939; Anterior Pituitary Fractions and Carbohydrate Metabolism; I. The Preparation and Properties of Diabetogenic Extracts, *J. Endocrinol.* **1**:339-355 (Nov.) 1939.

107. Young, F. G.: The Pituitary Gland and Carbohydrate Metabolism, *Endocrinology* **26**:345-351 (Feb.) 1940.

diabetogenic; although the injection of such extracts may induce a high degree of insensitivity to insulin, the fasting level of blood sugar may be virtually unchanged. Young is not of the opinion that this substance is identical with prolactin, with the thyrotropic, gonadotropic or ketogenic principle of the anterior lobe or with the melanophore-expanding substance from the pars intermedia. Since the glycotropic principle is not diabetogenic in normal animals, it is not identical with the diabetogenic principle, although it may be a constituent of the diabetogenic complex. This glycotropic principle has not yet been distinguished from a number of other pituitary fractions. He questioned whether there was a separate ketogenic factor or whether this was simply a part of the diabetogenic principle.

Diabetogenic Action of Extracts of the Anterior Lobe of the Pituitary Gland.—The ability of crude extracts of the anterior lobe to induce symptoms of diabetes in normal animals is lost if the glands are allowed to remain at room temperature for some hours prior to extraction; however, administration of the heat-stable substances of the anterior lobe to hypophysectomized depancreatized animals may cause an increase in glycosuria. The diabetogenic principle may be made up of two parts, one of which is heat labile and the other heat stable; the latter has an extrapancreatic action. In dogs in which diabetes was induced by anterior pituitary extract, the rate of secretion of insulin is diminished. This decrease may be due to partial exhaustion of the secretory mechanism of insulin, brought about by maintenance of high levels of blood sugar by extrapancreatic means, or it may be due to the direct effect of the diabetogenic principle of the anterior lobe of the pituitary gland on the islands of Langerhans.

If anterior pituitary extract is given daily to dogs for seven or more days, hyperglycemia and glycosuria do not occur for three to five days. The sensitivity of the animal to the hypoglycemic effect of insulin decreases during this period, even though the level of blood sugar is not much increased. After the latent period, glycosuria, ketonuria, polyuria, polydipsia and hyperlipemia occur and there is an increase in the animal's weight. The normal levels of glycogen in the liver may be maintained during the diabetes. Continued administration of anterior pituitary extract often fails to prevent the level of blood sugar from decreasing to normal and the diabetic condition from disappearing, although the animal remains relatively insensitive to insulin. A second rise in the level of blood sugar may be caused by increasing the amount of extract given, but this effect, too, disappears. However, in some cases the daily injection of extracts of the anterior lobe for long periods may cause a diabetic condition which does not disappear when the injections are discontinued. This happens if the dose is large enough or if the

amount injected daily is increased every few days. The following generalizations can be made in instances of this permanent diabetes: 1. There are no spontaneous remissions, and ketonuria may increase over a period of a year after cessation of the injections. 2. Dogs can survive for long periods without insulin and, with sufficient food, maintain their weight. 3. If insulin is given and then its administration is ceased, the animal may die in a state resembling diabetic coma. 4. Some dogs may require more insulin to control glycosuria than depancreatized dogs do under similar conditions. 5. On a diet of beef suet only, glycosuria and ketonuria are decreased. 6. The islands of Langerhans reveal histologic changes which include hydropic degeneration and hyalinization. Like the glycotropic substance, this diabetogenic principle has not been shown to be identical with prolactin, with the thyrotropic, glycotropic or gonadotropic substances of the anterior lobe or with the melanophore-expanding substance of the pars intermedia; neither has it been distinguished clearly from the ketogenic, glycostatic or adrenotropic substances. Young expressed the opinion that this principle is not the same as Collip's metabolism-stimulating factor.

Young also reviewed certain facts concerning the possibility of pancreatropic action of anterior pituitary extracts. Results of work performed by himself and by others indicate that frequent injections of an extract of the anterior lobe will produce an increase in the size and number of islets in the pancreas. Under the same conditions, the content of insulin in the pancreas of the rat may increase greatly. He felt that these results might explain the refractoriness to the diabetogenic action of extracts of the anterior lobe.

Young commented on whether there is a separate diabetogenic principle and pointed out many similar features between the diabetogenic and the growth principle. He felt that the growth-promoting action of the extracts of the anterior lobe may be due to ability of the pancreas to secrete sufficient insulin to induce retention of nitrogen and to promote oxidation of carbohydrate. If the pancreas is able to do this, as it is in the rat, then the extracts promote growth; if the available insulin is insufficient to prevent breakdown of proteins, then glycosuria and diabetes result. In the dog, the diabetogenic action may disappear if the islet tissue eventually is stimulated (by the pancreatropic effect of the extract) to produce insulin to overcome it.

Jensen and Grattan¹⁰⁸ discussed the identity of the glycotropic or anti-insulin substance of the anterior lobe of the pituitary gland. They concluded that the glycotropic effect of the anterior lobe of the pituitary

108. Jensen, H., and Grattan, J. F.: The Identity of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, *Am. J. Physiol.* **128**:270-275 (Jan.) 1940.

was produced by the adrenotropic factor. Regardless of the name or nature of this hormone, the fact remains that there is in the anterior lobe a principle which has an effect on the pancreas. This effect has been studied by many authors, a few of whom are listed.¹⁰⁹ Haist, Campbell and Best¹¹⁰ recently discussed the possibility of preventing diabetes among children who were likely to have it by administration of small doses of insulin, together with a diet low in carbohydrate and protein and high in fat. Results on experimental animals (rats, dogs and cats) indicated that affording the pancreas the benefit of physiologic rest by these means could improve a diabetic condition by reducing the strain on the remaining islet cells and also by permitting restoration to normal function of some of the exhausted islet cells. The authors explained that after partial pancreatectomy or during prolonged administration of anterior pituitary extracts, the islets were subjected to overstrain, and consequently they underwent hydropic degeneration. If insulin was given during this period of overwork, diabetes often was prevented.

Harrison and Long¹¹¹ studied the effects of anterior pituitary extract on the fasting rat. The injection of saline extracts of anterior lobes of pituitary glands of cattle into fasting normal or adrenalectomized rats was followed by a diminished excretion of nitrogen in the urine and by ketonuria. At the same time, hypoglycemia and a marked reduction in the nonprotein nitrogen of the blood were also found. Hypoglycemia developed in fasting adrenalectomized rats given large amounts of sodium chloride and sodium bicarbonate intraperitoneally, and the excretion of nitrogen in the urine was less than normal. The association of a decreased excretion of nitrogen and hypoglycemia suggested to the authors that the reduction in blood dextrose might be the result of diminished glyconeogenesis from protein, due to inhibition of protein catabolism. The changes in the blood dextrose of fasting adrenalectomized rats might also be explained on the basis of inadequate glyconeogenesis from protein following the loss of cortical hormone.

109. Dohan, F. C., and Lukens, F. D. W.: Antihormone Effects in Pancreatic Diabetes, *Proc. Soc. Exper. Biol. & Med.* **42**:167-171 (Oct.) 1939. Soong, H. Y.: The Assay of the Insulin Content of the Pancreas in Rats Receiving Anterior Pituitary Extract, *Chinese J. Physiol.* **15**:335-341 (June 30) 1940. Best, C. H.; Campbell, J., and Haist, R. E.: The Effect of Anterior Pituitary Extracts on the Insulin Content of the Pancreas, *J. Physiol.* **97**:200-206 (Dec. 14) 1939. Richardson, K. C.: Influence of Diabetogenic Anterior Pituitary Extracts on the Islets of Langerhans in Dogs, *Proc. Roy. Soc., London, s.B* **128**:153-169 (Jan. 4) 1940.

110. Haist, R. E.; Campbell, J., and Best, C. H.: The Prevention of Diabetes, *New England J. Med.* **223**:607-615 (Oct. 17) 1940.

111. Harrison, H. C., and Long, C. N. H.: Effects of Anterior Pituitary Extracts in the Fasted Rat, *Endocrinology* **26**:971-978 (June) 1940.

Russell⁶ reviewed the relation of the anterior lobe of the pituitary gland and the adrenal cortex to the metabolism of carbohydrate. In summary, she stated that in normal rats fed dextrose both whole anterior pituitary extract and adrenal cortex extract when given in large amounts appeared to depress the utilization of carbohydrates and to promote the deposition of glycogen. The former increased storage of glycogen in muscle only, and the latter more markedly affected the stores of glycogen in the liver. An adrenotropic extract of the anterior lobe of the pituitary, which contained the metabolic factors, also depressed the oxidation of carbohydrates and increased the deposition of glycogen in muscle. In adrenalectomized rats, large amounts of adrenal cortex extract increased the glycogen in the liver at the expense of oxidation but did not affect the glycogen in muscle; however, anterior pituitary extract given in the presence of adrenal cortex extract resulted in the usual action of the extract on oxidation and muscle glycogen, even though the dose of cortical extract itself was too small to be effective. The two extracts apparently had a synergistic and complementary effect on the metabolism of dextrose fed to rats. In fasting rats the anterior pituitary extract maintained levels of glycogen in muscle in the absence of the adrenal cortical extract without affecting the amount of glycogen in the liver or the blood sugar, whereas cortical extract, probably by promoting glyconeogenesis, increased stores of glycogen in the liver and maintained levels of blood sugar, although it did not seem to affect directly the stores of glycogen in muscle.

Flint¹¹² published some interesting observations on hypophysial diabetes and the action of the so-called Macallum-Laughton synergist. He stated:

As it stands, diabetes represents a derangement in the normal antagonism and regulation exercised by the anterior pituitary and the pancreaticoduodenal ensemble upon the control and regulation of the sugar exchange as well as the wider field of the intermediate carbohydrate metabolism. This glucopathy is its major characteristic symptom.

He contended that under normal conditions the chief hypoglycemic factor is insulin, which primarily governs the utilization and storage of sugar. The stabilization of the glycemic level through static action and an anchor effect is mediated by the Macallum-Laughton synergist, which normally checks hyperglycemia or hypoglycemia for either a long or a short term and acts synergistically with insulin. Flint considered that its therapeutic action consisted in producing these effects in long symmetric patterns in the blood sugar curve, which might last for months.

112. Flint, J. M.: *Further Observations on Hypophyseal Diabetes and the Action of the Macallum-Laughton Synergist*, London, A. B. Macallum, 1939.

Paschkis and Schwoner¹¹³ reported that the feeding of protein was followed by the output in the urine of a factor which when injected into rats produced a decrease of the nonprotein nitrogen constituents of the blood. This reaction may be obtained by injection of an alkaline extract of the anterior lobe of the pituitary gland. These authors expressed the opinion that the factor in the urine originated in the pituitary gland.

Farr and Alpert¹¹⁴ studied the effects of various endocrine extracts on the amino acids in the blood and reported incidental findings as to the blood sugar and urea. They concluded that intravenous injection of extracts containing the growth and metabolic factors of the anterior lobe of the pituitary, or of pitressin, chorionic gonadotropin (antuitrin S), adrenal cortex extract, testosterone propionate or thyroxin, was followed by marked decreases in the concentration of amino acids in the blood plasma. The intraperitoneal injection of an extract containing the growth factor of the anterior lobe of the pituitary produced a transient fall of the amino acids in the plasma. These findings were not accompanied by significant or consistent changes in the amount of sugar or urea in the blood. Subcutaneous injection of insulin or of epinephrine hydrochloride produced sharp decreases in the plasma amino acids, with a mutually opposite effect on the level of blood sugar. The changes in the plasma amino acids after injection of insulin were not accompanied by a corresponding change in the amount of amino acids in the cells.

Diabetes Insipidus and the Antidiuretic Principle of the Posterior Lobe of the Pituitary Gland.—Fisher¹¹⁵ reviewed the knowledge of diabetes insipidus and of the neurohormonal control of water balance. Both the hypothalamus and the pituitary gland are concerned in the maintenance of water balance. Diabetes insipidus has a complex etiology. Alterations in both the hypothalamus and the pituitary gland and in the connection between the two, which involves the hypothalamic nuclei with their axons to the neurohypophysis, are the causative factors. Fisher referred to the hypothalamohypophyseal system, which consists of certain hypothalamic nuclei, axons to the neurohypophysis and the neurohypophysis itself, including the median eminence, the infundibular stalk and the infundibular process. As the result of detailed studies, he reported that injury to any part of the hypothalamohypophyseal system was reflected by the presence of degenerative changes in other parts of

113. Paschkis, K. E., and Schwoner, A.: The Output of Protein Metabolism Hormone of the Pituitary Anterior Lobe, *Endocrinology* **26**:117-122 (Jan.) 1940.

114. Farr, L. E., and Alpert, L. K.: The Effect of Endocrine Extracts on the Amino Acids in the Blood with Incidental Findings on the Blood Sugar and Urea, *Am. J. Physiol.* **128**:772-781 (March) 1940.

115. Fisher, C.: Diabetes Insipidus and the Neurohormonal Control of Water Balance, *Proc. Inst. Med. Chicago* **13**:117-119 (May 15) 1940.

the system. Diabetes insipidus is a hormonal disturbance attributable to deficiency in the production of the antidiuretic principle by the neurohypophysis. It is a nervous disturbance so far as lesions of the hypothalamus result in changes in the neurohypophysis. The atrophic neurohypophyses from cats with diabetes insipidus were markedly deficient in antidiuretic, pressor and oxytocic activity. Neurohypophysial extracts are antidiuretic. Initially, polyuria and polydipsia result. Then there is a 'normal phase, after which diabetes insipidus becomes permanent. Polyuria precedes polydipsia. The anterior lobe (pars distalis) of the pituitary gland exerts a diuretic effect. Thyroidectomy temporarily inhibits diabetes insipidus. Thyroid and sodium chloride have a greater diuretic effect on diabetic than on normal animals. Castration and pregnancy produce little change in diabetes insipidus. The pars nervosa rather than the pars intermedia of the pituitary gland elaborates the active principles of the so-called posterior lobe. The supraopticohypophysial portion of the hypothalamohypophysial system regulates the secretion of the antidiuretic principle by the neurohypophysis. This principle acts chiefly on the kidney and prevents excretion of excessive amounts of urine. Polyuria is due to diuretic processes in the body unchecked by the antidiuretic mechanism. The diuretic processes are the result of activity of the anterior lobe. This activity is due to general control over metabolism rather than to a specific diuretic hormone. This relation of the pituitary gland and water diuresis has been reviewed in an editorial.¹¹⁶

Baker and Craft¹¹⁷ described the observations at necropsy in the case of a pituitary dwarf, 18 years of age, who had severe and permanent diabetes insipidus and who had been studied for eight years. Bilateral destructive lesions limited almost exclusively to the region occupied by the supraoptic nuclei were found. Most of the destruction was in the lateral walls of the optic recess. The neurohypophysis was replaced completely by hyalinized connective tissue. Kylin¹¹⁸ reported hypophysial transplantation in a case of diabetes insipidus. The patient was a woman, 22 years of age, who had received an injection of finely divided hypophysial gland into the gluteus muscle. He stated that improvement occurred but did not indicate how long it lasted.

116. The Pituitary Gland and Water Diuresis, editorial, J. A. M. A. **113**: 2322-2323 (Dec. 23) 1939.

117. Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, *Endocrinology* **26**:801-806 (May) 1940.

118. Kylin, E.: Hypophysentransplantation in einem Fall mit Diabetes insipidus, *Acta med. Scandinav.* **101**:566-567, 1939; abstracted, *Endocrinology* **26**:933 (May) 1940.

Treatment of Peptic Ulcer with Posterior Pituitary Preparation.—Metz and his associate¹¹⁹ reported their results in the treatment of peptic ulcer with posterior pituitary preparations. They obtained satisfactory clinical results in 76 cases of peptic ulcer. Intranasal insufflation of posterior pituitary in powdered form proved to be the most satisfactory mode of administration. This reference is included because of the obvious importance of having further work of this type conducted under careful control.

Hypopituitarism and Simmonds' Disease.—Magendantz and Proger¹²⁰ discussed the differential diagnosis of anorexia nervosa and hypopituitarism. Many reports of Simmonds' disease, or pituitary cachexia, continue to be recorded in the literature, and many conditions apparently examples of this disease continue to be diagnosed more properly as anorexia nervosa. Simmonds' disease is one of the rarest conditions known; anorexia nervosa is much more common. The fact that these two conditions simulate each other so closely undoubtedly explains the incorrect use of the term Simmonds' disease for the more common condition of anorexia nervosa.

OBESITY

The current literature on obesity is concerned chiefly with the extremely controversial subject of the pathogenesis of this condition. Obesity is considered by different observers to be either exogenous or endogenous. Those who maintain that excessive weight is exogenous, that is, that obesity represents an imbalance between the intake of food and the output of energy, point out that the most effective treatment is ingestion of a diet low in calories and that no endocrine preparations available can by themselves bring about the same therapeutic result. On the other hand, observers who maintain that obesity is the result of endogenous disturbances have presented an imposing array of data to support their contention that disorders of one or several of the factors, endocrine and otherwise, which control fat metabolism are operative in accumulation of excessive body weight. However, supporters of the endogenous theory are not at all in agreement as to the site of disturbance. Some observers deny that the abnormality is localized in the endocrine system, while others attribute to the endocrine system a major role in the pathogenesis of obesity. Furthermore, there is no uniformity of opinion as to the gland, or group of glands, primarily

119. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Preparations: Clinical and Experimental Observations, *Am. J. Digest. Dis.* 7:27-32 (Jan.) 1940.

120. Magendantz, H., and Proger, S.: Anorexia Nervosa or Hypopituitarism? *J. A. M. A.* 114:1973-1983 (May 18) 1940.

involved. Several excellent reviews of the etiology of obesity have appeared recently.¹²¹ Space does not permit more than a few citations from these works.

Rony ^{121a} included in his monograph a report on his own series of obese patients, both juvenile and adult. A search was made for endocrine abnormalities; diagnosis of glandular disorder was based on the history, on observations pertaining to the growth and sexual and mental development of the patient and, finally, on data obtained by such laboratory procedures as determination of the basal metabolic rate, the dextrose tolerance test and roentgenographic study of the sella turcica and the bones of the hands. The juvenile group consisted of 22 boys and 28 girls between the ages of 7 and 16 years whose average weight was 54 per cent above normal. Only 6 of this entire group, as judged by results of the aforementioned examinations, were considered entirely free of endocrine disturbance. In the majority of instances, various combinations of abnormalities were present; in 68 per cent of cases these abnormalities were considered the result of glandular disturbance. The adult group included 192 women and 8 men; the average age was 31 years and the average weight was 66 per cent above normal. Definite endocrine syndromes were found in only 13 cases, and a diagnosis of probable endocrine disturbance was made in 56. In many of these, the exact localization of the glandular disturbance could not be determined. Of the adult patients, 131 were apparently free from endocrine disturbance.

Goldzieher ^{121b} discussed the role that each of the endocrine glands could play in the pathogenesis of obesity; he concluded that, although hypothyroidism and adrenal insufficiency rarely play a major role in obesity, the gonads may in some instances be held responsible, especially in obesity occurring at the menopause. The anterior lobe of the pituitary gland is of considerable importance in connection with obesity of the girdle type. He further pointed out that in connection with obesity of the so-called pituitary type, retention of salt and water associated with an excessive appetite (possibly caused by hypoglycemia) may add to the excessive weight.

On the other hand, Bauer ¹²² stated that the etiologic factor in obesity is "in a very small number of cases an endocrine disturbance." Hetherington ¹²³ reported that he injected chromic acid into the

121. (a) Rony, H. R.: *Obesity and Leanness*, Philadelphia, Lea & Febiger, 1940. (b) Goldzieher, M. A.: *Obesity*, *M. Rec.* **151**:98-100 (Feb. 7) 1940. (c) Freed, S. C.: *Modern Concepts of Obesity*, *Illinois M. J.* **77**:282-284 (March) 1940.

122. Bauer, J.: *Common Diagnostic and Therapeutic Errors in the Management of Fat Boys*, *M. Rec.* **151**:89-92 (Feb. 7) 1940.

123. Hetherington, A. W.: *Obesity in the Rat Following Injection of Chromic Acid into the Hypophysis*, *Endocrinology* **26**:264-268 (Feb.) 1940.

hypophyses of rats in an attempt to check the possibility that some sort of selective deterioration of the hypophysis might be responsible for pathologic adiposity. Few animals so treated disclosed any perceptible degree of excess deposition of fat; necropsy on those animals which did become overweight revealed considerable hypothalamic damage in addition to destruction of the hypophysis. In subsequent experiments in which hypothalamic lesions were made without involving the hypophysis, almost 100 per cent of the animals became obese. Hetherington concluded that perhaps lesions in the hypothalamus or in a hypophysial-hypothalamic pathway may be of importance in the pathogenesis of obesity.

A wide variety of other theories have appeared in the literature and are considered fully in Rony's review. Briefly, obesity is attributed to one of the following conditions: (1) disturbance in the nervous system, including both the cerebrospinal and the autonomic division; (2) disturbance in the intermediary metabolism of both fat and carbohydrate; (3) an inherited "abnormal anlage for obesity" (Bauer),¹²² or (4) variation in the tendency of the adipose tissue to accumulate fat (lipophilia). In this last hypothesis it is assumed that the adipose tissue of the obese person differs from that of the normal person in that it has a greater tendency to accumulate fat and a greater resistance to the mobilization of fat. The majority of authors concluded that none of these theories may be applied to all, or even to a large percentage of, obese patients. Whatever the etiologic factor is the greater number of these patients will respond to a restricted diet without the addition of endocrine preparations or roentgen therapy. Sprague and one of us (E. H. R.)¹²⁴ recently discussed in detail a restricted diet, consisting of approximately 585 calories a day, which was found to give excellent results among a considerable number of extremely overweight persons. Such a diet must be supplemented with concentrates of vitamins and calcium.

A good deal of discussion also has appeared in the literature in regard to the relation of obesity to glycosuria. Two or three years ago, Newburgh and Conn¹²⁵ reported that middle-aged obese people could have glycosuria in the absence of other symptoms of diabetes and that this would disappear with reduction of weight and would not recur even with an increase in consumption of carbohydrate, provided that there was not a concomitant gain in weight. Recently, Embleton¹²⁶ reported

124. Rynearson, E. H., and Sprague, A. W.: Obesity, California & West. Med. **53**:158-162 (Oct.) 1940.

125. Newburgh, L. H., and Conn, J. W.: A New Interpretation of Hyperglycemia in Obese Middle-Aged Persons, J. A. M. A. **112**:7-11 (Jan. 7) 1939.

126. Embleton, D.: Glucose-Tolerance Curves in Five Hundred Obese Cases, Brit. M. J. **2**:739-740 (Oct. 8) 1938.

that of 242 obese males 73 per cent had high dextrose tolerance curves, although only a small number had glycosuria. This tendency toward a diabetic type of tolerance curve was much more apparent in males over 35 years old.

Chaikoff and Connor¹²⁷ reported that in depancreatized dogs receiving diets high in fat the continued presence of excessively high amounts of fat in the liver for several months stimulated hepatic fibrosis, even to the extent of causing death. Wood and Cash¹²⁸ reported that excessive weight may be an important factor in elevation of the systolic blood pressure.

127. Chaikoff, I. L., and Connor, C. L.: Production of Cirrhosis of the Liver of the Normal Dog by High Fat Diets, *Proc. Soc. Exper. Biol. & Med.* **43**:638-641 (April) 1940.

128. Wood, J. E., Jr., and Cash, J. R.: Obesity and Hypertension: Clinical and Experimental Observations, *Ann. Int. Med.* **13**:81-90 (July) 1939.

Correspondence

PINEALECTOMIES ON YOUNG MAMMALS

To the Editor:—My attention has been called to an article by Weinberger and Grant entitled "Precocious Puberty and Tumors of the Hypothalamus," in the April issue of the ARCHIVES, page 762.

In this article the authors have completely misinterpreted and misstated the work by Dr. Martin and me on the experimental removal of the pineal gland in young mammals, a report of which appeared in the January 1940 issue of the *Archives of Neurology and Psychiatry*, page 23, and to which they refer.

Weinberger and Grant state (page 763): "Davis and Martin performed pinealec-tomies on rats and cats. In the former they saw no evidence of sexual precocity but claimed that they did so in cats. This opinion was based on observations on only 3 cats out of the 14 that survived the operation." As a matter of fact, we stated in our article that our series of cats consisted of 71 animals, of nineteen litters, none of which died from effects of the operation. At the time the article was in press, 14 animals were *then* under observation, but our paper was based on the collected observations on 71 animals, which a careful perusal of the article would have shown. The statement that only 3 cats out of 14 survived and were the basis for the article is, therefore, entirely erroneous. Graphs were shown of changes in 5 animals which were used for illustrative purposes.

Again, Weinberger and Grant state (page 763): "Many workers in addition have performed the same experiments as Davis and Martin, with opposite results." A careful reading of the enormous literature on this subject will show that this, too, is untrue. Animals as high in the mammalian scale as cats have never been operated on before they were mature. Our experiments were the first of the kind on kittens 6 weeks old. Extirpation of the pineal gland by the Horsley-Clark apparatus had never been done before on any animals, regardless of age. In our opinion, removal of the gland by this method obviated any possible damage to neighboring structures; this our photomicrographs clearly show. Consequently, our observations were made on animals with no other lesion than complete removal of the pineal gland.

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Book Reviews

Bacillary and Rickettsial Infections. By William H. Holmes, M.D., Professor of Medicine, Northwestern University Medical School. Price \$6. Pp. 676. New York: The Macmillan Company, 1940.

For the student of internal medicine Dr. Holmes has written an avowedly unconventional textbook. Sensitively aware that the present medical curriculum, with its vast offering of clinical and laboratory technics, tends often to produce the mechanic, rather than the cultivated, wise and skilful physician, the author has dealt with certain of the major infectious diseases from the broadest possible point of view. With this attitude in mind one finds it easy to understand the inclusion of the large amount of historical material, which, parenthetically, is well chosen, the many instructive epidemiologic discussions, the outlines of preventive measures and much information concerning etiologic and pathologic aspects of such infections. But, on this account it must not by any means be assumed that clinical aspects are neglected. The problems of diagnosis and treatment of the disease in the individual patient, however, are brought into a just relationship to its natural and written history. In the author's definition of this relationship not only are these immediate concerns of the physicians illuminated in a manner possible in no other way, but the author's primary objective of presenting certain of the fundamental data of internal medicine in a manner to enlarge the vision of the student is not infrequently attained.

The volume is broken up into sections on the following subjects: pasteurelloses, including plague and tularemia; the rickettsial diseases; brucelloses; enteric infections; bacillary intoxications, under which heading diphtheria and diseases caused by the exotoxigenic anaerobes are dealt with; diseases due to the hemophilic bacteria, and mycobacterial diseases, including an extensive account of the essential facts concerning tuberculosis. Finally, there is a chapter on a variety of rare or less important bacillary infections, such as anthrax and glanders.

At first this choice seems rather surprising, since it omits many infections of the greatest significance. It is also a little difficult to perceive why the description of the rickettsial diseases—so similar as regards their etiologic agents to the virus diseases—should have been inserted between the chapters on plague and tularemia and those on the brucella infections.

This quandary is answered in part by the author's implication that a similar book dealing with infections of coccic, spirochetal and protozoal origin will be published subsequently. Possibly the epidemiologic similarities of typhus and such pandemic scourges as plague and cholera form a good reason for such treatment of the rickettsial diseases.

Errors of fact are extremely few, in spite of the many different fields of investigation from which the author has drawn his material. The factual content, moreover, is abundant when one considers the scope and the general purpose of the book. But it represents a bare minimum for the medical student, who would require, in addition, a more conventional textbook of medicine and certainly standard texts on bacteriology and parasitology. The book will increase the technical knowledge of the pathologist, the bacteriologist and the professional student of epidemics, but these specialists will profit in other ways.

Dr. Holmes deserves much praise for the clear and lively manner in which he has presented these descriptions of infectious disease and for his successful attempt to maintain in this mechanistic age the humanistic tradition which has always characterized the great physicians of the past.

A Symposium on the Blood and Blood-Forming Organs. Price, \$3.50. Pp. 264, with illustrations. Madison, Wis.: The University of Wisconsin Press, 1939.

The book is a collection of the papers presented at the Institute for Consideration of the Blood and Blood-Forming Organs held at the University of Wisconsin, Sept. 4 to 6, 1939. In keeping with the stated purpose of the institute, basic principles and newer fundamental scientific aspects of hematology are stressed. The authors, fifteen in number, are all representative leaders in their fields.

Watson presents the recent work on the porphyrins, a field which has been neglected because of the technical difficulties involved. Rhoads reports on a study of "all cases of refractory anemia as they were referred to the [Rockefeller] institute." The study is important because of its comprehensiveness and the conclusions. Articles by Heath on anemia caused by iron deficiency, by Minot on anemia of nutritional deficiency and by Diamond on erythroblastic anemia ably cover these subjects.

Meulengracht describes experimental work concerning the fundamental defect in pernicious anemia. Investigative work on hemolytic anemia is presented by Haden; the work on experimental leukemia, by Furth, and the work on bone marrow cultures, by Osgood.

Forkner presents the topics of monocytic leukemia and subleukemic leukemia with perhaps too little consideration of the distinction between the Nägeli and the Schilling type of monocytic leukemia; he may also place too much emphasis on the "supravital" technic and the oxidase or peroxidase reaction.

There are excellent reviews of Hodgkin's disease by Krumbhaar and of infectious mononucleosis by Downey. Reznikoff, in addition to recording the usual information concerning polycythemia vera, describes his finding in the bone marrow of thickened capillaries and adventitia and subintimal fibrosis of arteries and arterioles.

Doan points out clinical applications of knowledge of the reticuloendothelial system, and Eagle describes the various theories of blood coagulation and the clinical uses of heparin and vitamin K.

As would be expected, much of the material included has been published elsewhere, and in some instances in more detail, but the book serves a definite purpose, since each of the topics has been presented as an entity and has been brought up to date. The inclusion of a satisfactory bibliography with most of the articles augments their value. An index would have been a useful addition but is not essential to this type of book.

Hemorrhagic Diseases. By Kaare K. Nygaard, M.D. Price, \$5.50. Pp. 320, with 59 illustrations. St. Louis: C. V. Mosby Company, 1941.

Nygaard has written a splendid monograph on hemorrhagic diseases. The greater part of the book (almost 200 pages) is devoted to results of experimental and laboratory studies, and only the last, or third, section deals with the hemorrhagic diseases from the clinical point of view.

In part I the author discusses the method of determining the coagulability of the blood, elaborates on the photoelectric principle and goes into detail in the succeeding chapters concerning photology. The coagulability of blood plasma, the interaction of thrombin and fibrinogen and the coagulant effect of thromboplastin are treated in part II.

To the laboratory worker and the hematologist the monograph should be of inestimable value. The material is presented in a clearcut manner and is adequately illustrated with charts, diagrams and tables. In addition, there is an extremely complete review of the literature. Some of the relatively short chapters have as many as 120 references.

The third section of the book contains a mass of data which are and should be of interest to the clinician. However, this section is relatively short (slightly less than 100 pages) and probably would not be of sufficient value to the clinician to

warrant his making regular use of the book. As a matter of fact, it seems to the reviewer that part III might have been omitted, or else enlarged. It is doubtful if it is of any particular use to the hematologist in the laboratory, although the greater part of the book would interest him, and not the clinician.

Felicitations are due the author for his splendid treatise on blood coagulation. The data and facts he gives are based on personal experience and on the work of others. He has gathered together most of the known material germane to the study of the coagulation of the blood and has presented it in an attractive, albeit scientific, manner. The reviewer does wish, however, that Nygaard had not appended the anemic part III.

Cardiologia (Cardiology). By Jorge Meneses Hoyos, professor at the Mexico School of Medicine and head of the Cardiology Department of the Military General Hospital. Pp. 277. Mexico City: Editorial Cultura, 1939.

The author approached the task of writing this book with the main idea of offering medical students a modern textbook and a ready source of information on the most recent advances in the subject of cardiology. The result, however, is also splendidly adapted to the average practitioner who may wish to bring himself up to date.

All the chapters are concise and to the point, summarizing ably the main characteristics of the anatomic, physiologic, physical diagnostic, roentgenologic and electrocardiographic aspects of the problem. The author does not seem to follow any specified classification and is apparently taxed at times to reconcile the English, French and German points of view. He initiates the description of the pathologic manifestations of the heart with rheumatic infection. He next deals with endocarditis and pericarditis, valvular lesions, congenital diseases and cardioaortic syphilis. The chapter on arteriosclerosis is followed by one on myocardial lesions. The section dealing with secondary cardiopathic conditions is brief and interesting, comprising such cardiac disturbances as follow hypertensive, pulmonary, endocrinologic, obese or anemic conditions. A short reference to cardiac neuroses is followed by discussions of disturbances of cardiac rhythm, cardiac insufficiency and angina pectoris and by one final section on peripheral vascular diseases. Considering the vastness of the topic, the author has limited himself with ability, and his students no doubt will be grateful for the clearcut sketches he has presented. Each chapter is followed by a well selected bibliography, serving as a leader for further and deeper study.

Tratado de quimica normal y patologica de la sangre. By L. Corona, Professor of Chemical Physiology, University of Chile. Second edition. Pp. 944, with 155 illustrations. Santiago de Chile: Ercilla, 1940.

The first edition of this handbook appeared in 1937, and now the second edition is forthcoming. Each edition was written for the clinician as well as the laboratory worker and was designed to explain to the former as simply as possible the underlying physiologic basis for the various laboratory tests that can be performed on blood and to describe for the latter reliable methods for carrying through the different procedures.

The volume represents painstaking work. Eleven hundred and eighty references are given, and by glancing through them it is evident that the author has attempted to keep his information as up-to-date as possible. Among new material, vitamin K, Gibson's dye method for determining blood volume and photoelectric colorimetry are discussed; on the other hand, if the number of references to a man's publications mean anything, the pioneer work in chemical biochemistry of North American investigators has received due recognition. Benedict is referred to eight times, Cullen eleven times, Folin twenty-five times, Henderson thirty times and Van Slyke thirty-one times.

A book of this nature written in Spanish is likely to be more popular south of the border than in the north. The ARCHIVES, however, is glad to acknowledge

such a meritorious publication from a friendly neighbor. The text is clearly written. The illustrations and diagrams are excellent. The book as a whole cannot fail to be useful and much studied.

Herzkrankheiten: I. Physiologie, Beurteilung und funktionelle Pathologie des Herzens. By Prof. Dr. Max Hochrein. Price, 11 marks. Pp. 416. Dresden: Theodor Steinkopff, 1941.

In the foreword the author states that he does not hope to present an exhaustive study of heart disease, but attempts merely to outline his own views on this subject.

The first volume, in a series of three, deals with the physiologic, diagnostic and functional pathologic aspects of diseases of the heart. All are discussed in a clear and understanding manner, with a good correlation between theory and practice.

A 34 page bibliography, in which American authors are well represented, concludes the volume.

The two subsequent parts of this work on heart disease are to be entitled "Clinic on Coronary Disease" and "Therapy of Heart Disease."

Biologie der Grosstadt. By B. de Rudder and F. Linke. Price, 8 marks. Pp. 210, with 49 illustrations. Dresden and Leipzig: Theodor Steinkopff, 1940.

This paper-bound volume contains the transactions of the fourth conference held at Frankfurt on the Main, Germany, on May 9 and 10, 1940. There are, in all, twenty papers dealing with various changes which would improve general conditions in a large city. Such titles as "Climate and the City," "The Beginning and Growth of a City," "Characteristics of Industrial Towns," "Nutrition of the City Dweller" and "Nutrition and Incidence of Peptic Ulcer" are an index to the wide variety of topics covered.

The book is of interest so far as it gives an insight into the thought on this subject in wartime Germany.

Age Morphology of Primary Tubercles. By Henry Sweaney, M.D. Price, \$5. Pp. 265, with 73 plates, 26 charts and 7 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

It is the author's thesis that if one can establish certain characteristics of a tubercle in relation to its age, then one can deduce from the character of the tubercle the age of the infection, with the various clinical and epidemiologic implications. Whether or not this project is actually workable the reader must decide for himself, but in any event the book contains a mass of interesting factual data on the morphologic aspects of tubercles. There are numerous photomicrographs and reproductions of roentgenograms and diagrams, and the general format is of the best.

The Role of the Liver in Surgery. By Frederick Fitzherbert Boyce, M.D. Price, \$5. Pp. 365, with 44 illustrations and 25 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1940.

In this handsomely printed and profusely illustrated monograph the writer has assembled a great deal of material pertaining to the liver of special interest to the surgeon. Liver function tests from the standpoint of preparation for operation, vitamin K, hepatic function in thyroid disease and, above all, the dreaded and mysterious "liver death" occurring after operation are discussed in detail. There is much in this book of interest, even though it is really a collection of loosely related essays, rather than a systematic treatise.

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MULTIPLE FRESH CORONARY OCCLUSIONS IN PATIENTS WITH ANTECEDENT SHOCK

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In a study of the clinical and pathologic findings in a series of 350 cases, we have observed multiple fresh coronary occlusions in a group of 11 cases. In 8 of these, multiple fresh thrombi had occluded the arteries; in the remaining 3 cases multiple occlusions were due to hemorrhages within the atheromatous plaque and to ruptured atheromatous abscesses. The hearts in these 11 cases were studied by the method of injection and dissection of the coronary arteries previously described.¹ The striking observation was made that all these instances of multiple fresh occlusions occurred in the presence of shock. A search of the voluminous literature on coronary thrombosis and myocardial infarction, as well as reference to the standard cardiologic texts, has failed to reveal any publications dealing with this correlation between shock and multiple coronary occlusion, although the existence of multiple fresh thrombi has been noted by several observers.² We therefore have studied this group of 11 cases in order to learn the clinical and pathologic significance of the phenomenon.

This investigation was aided by a grant from the Josiah Macy, Jr. Foundation.

Presented in abstract at the meeting of the American Heart Association, New York, June 7, 1940.

From the Departments of Medicine and Pathology, Beth Israel Hospital and Harvard Medical School.

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2. (a) Sprague, H. B., and Orgain, E. S.: Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital 1914-1934, *New England J. Med.* **212**:903, 1935. (b) Master, A. M.; Dack, S., and Jaffe, H. L.: Coronary Artery Thrombosis—Mode of Death and Analysis of Fatal Cases, *New York State J. Med.* **37**:1707, 1937. (c) Horn, H., and Finkelstein, L. E.: Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion, *Am. Heart J.* **19**:655, 1940.

METHOD

The technic used in injecting and dissecting the hearts has been described previously in detail ^{1a} and in summary form ^{1b} and will be here only briefly stated. The two coronary arteries were injected simultaneously, each with a differently colored, radiopaque, warm (45 C.) lead-agar mass under a pressure of 150 to 200 mm. of mercury. A red mass was injected into the right coronary artery and a blue mass into the left coronary artery.³ The mass was immediately hardened by immersion in iced physiologic solution of sodium chloride, and the unfixed heart was unrolled by a series of incisions so that all the coronary arteries lay in one plane. A roentgenogram of this preparation was made. At no place in the roentgenogram of the unrolled heart was there a shadow of more than a single thickness of the cardiac wall. A complete dissection of the injected, unfixed arteries was then carried out in order to confirm, correct or extend the observations recorded roentgenographically. Multiple representative sections of the myocardium were studied histologically.

Instead of presenting colored copies of the actual roentgenogram, we have prepared a tracing of the coronary arterial tree of each heart.^{1b} In making these diagrams the diameter of the vessels was exaggerated to permit the stippling and cross hatching which represent the red and blue colors, respectively. The areas of narrowing and occlusion indicated in these diagrams were disclosed by means of the injection, by the roentgenogram and, particularly, by the dissection.

All the old healed areas of occlusion were conclusively demonstrated by the dissection, which visualized the absence of any color from injection mass in the occluded portion after an artery was split open. The fresh thrombi were disclosed during the course of the dissection by carefully removing the injection mass found about them. Only thrombi which were definitely adherent to the vessel wall, and therefore clearly formed ante mortem, are considered in this report. Nonadherent, stringlike blood clots were not included because of the difficulty in determining whether or not they were formed ante mortem. Also excluded were those multiple thrombi in which one, by its anatomic location, might have resulted from embolization from the other.

RESULTS

The results of the study are summarized in table 1 and in the reports of 8 cases.

CASE 1.—*Clinical Data.*—A man 60 years of age had had angina pectoris for four years. Four days before death lobar pneumonia developed, for which he was hospitalized on the last day. Physical examination revealed a temperature of 102 F., a respiratory rate of 40 per minute, cyanosis, jaundice, consolidation of the lower lobe of the right lung, tachycardia, with a rate of 140 per minute, a rapid and thready pulse and a blood pressure of 100 systolic and 64 diastolic. Antipneumococcus serum (type VIII) was given every two hours because of the critical condition, despite a positive cutaneous reaction. Each injection was followed

3. In a few instances three differently colored injection masses were employed for the three main coronary arteries, but, for schematic purposes, only the original two color method is represented in the diagrams.

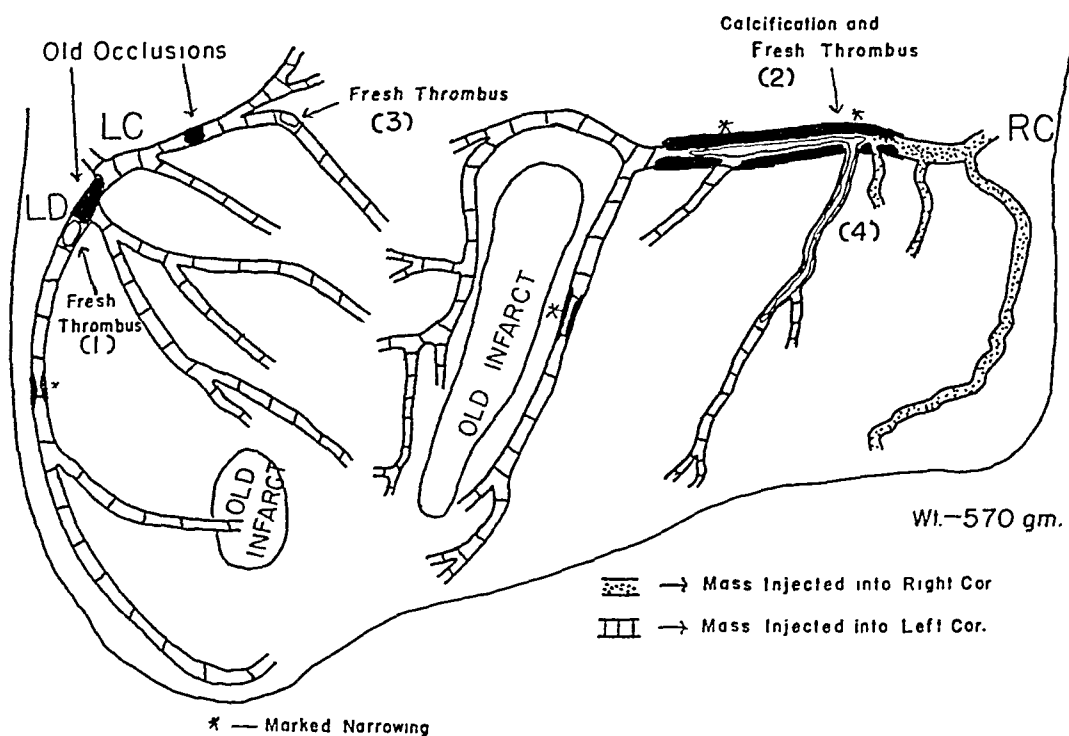


Fig. 1 (case 1).—Fresh adherent thrombi in (1) left anterior descending and (2) right coronary arteries and in primary branches of (3) left circumflex and (4) right coronary artery. In this and the succeeding figures, the following abbreviations are used: LD, left anterior descending coronary artery; LC, left circumflex coronary artery, and RC, right coronary artery.

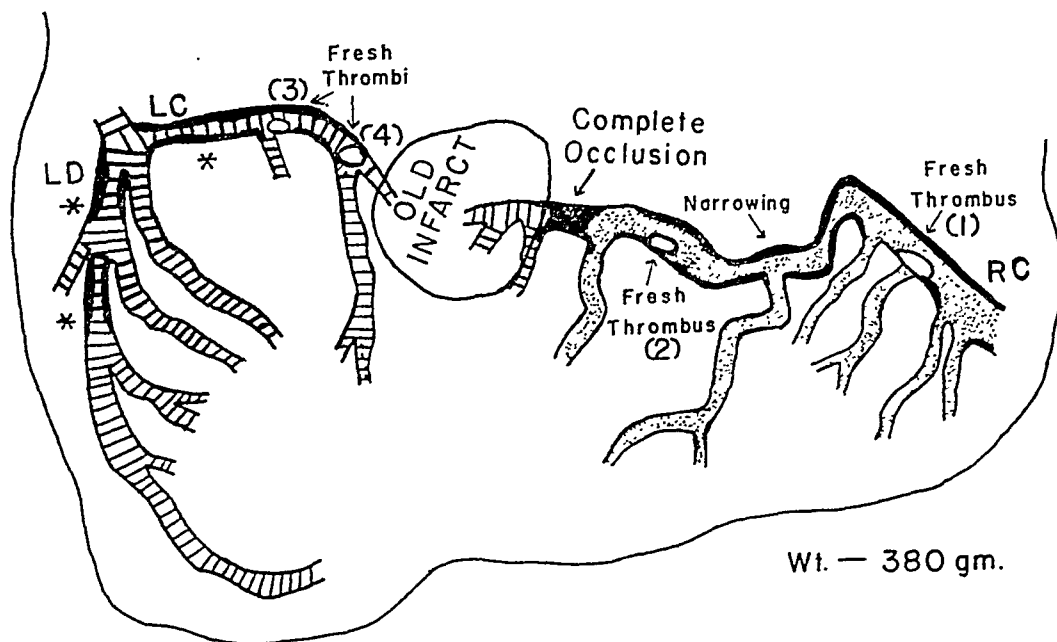


Fig. 2 (case 2).—Fresh adherent thrombi in (1 and 2) right and (3 and 4) left circumflex coronary arteries.

by squeezing substernal pain. Evidences of shock progressively increased until death occurred, twelve hours after admission.

Necropsy.—In the heart there were two healed left ventricular infarcts, situated anteriorly and posteriorly, respectively, with considerable fibrosis of the myo-

TABLE 1.—Data on Cases of

Case No.	Age	Sex	Weight of Heart, Gm.	Coro-nary Arterio-sclerosis	Old Coronary Occlusions			Fresh Coronary Thrombi			Myo-cardial Fi-brosis	Anasto-moses	Infarcts	Clinical Episodes of Myocardial Infarction	
					LD	LC	R	LD	LC	R				Past	Term-inal
1	60	M	570	+++	MC	M	—	MC	B	MC B	++	L-L L-R	Healed Healed	—	—
2†	69	M	380	+++	—	—	MC	—	MC MC	MC MC	+++	L-L L-R	Healed	—	—
3	69	F	680	+++	MC	M	—	—	B	MC	+++	L-L L-R	Recent	—	6 hr.
4	62	M	440	++	—	—	B	MC	—	B	—	L-L L-R	—	—	—
5†	59	M	685	+++	B	MC	B B	—	MC	MC Ma	+++	L-L L-R R-R	—	—	—
6†	68	M	620	+	—	—	—	MC B	—	—	—	L-L	Recent	—	—
7	69	M	550	+++	N	N	—	MC	MC	—	++	L-L L-R R-L	Recent	—	12 days
8	65	M	Normal	+++	—	B	MC	—	B	MC	++	L-L L-R	Recent	—	18 hr.

* In this table, LD, indicates left descending coronary artery; LC, left circumflex coronary artery; R, right coronary artery; +, slight; ++, moderate; +++, marked; MC, complete occlusion of major coronary artery; B, complete occlusion of primary branch of major coronary artery; Ma, atheromatous abscess occluding major coronary artery; N, marked narrowing of major coronary artery; L, left coronary artery; MS, mitral stenosis; MI, mitral insufficiency, and AS, aortic stenosis.

† This case is described more fully in a previous communication.^{1b}

cardium between them. A fresh endocardial thrombus formed ante mortem was attached to the smaller, anterior infarct.

The coronary arteries are diagramed in figure 1.

CASE 2.—*Clinical Data.*—A man 69 years of age had had angina pectoris for three and a half years and evidences of slight congestive failure and arterial hypertension, with a pressure of 180 systolic and 110 diastolic, for twenty-two months before death. Three days before death massive hematemesis, associated with an

*Multiple Fresh Thrombosis**

Cause	Val- vular Dis- ease	Duration of An- gina Pec- toris, Yr.	Conges- tive Heart Failure	Duration of Elevated Blood Pressure, Mm. Hg	Duration of Shock, Hr.	Cause of Shock	Evidence of Shock	Primary Clinical Diagnosis
Arterio- sclerosis	—	4	—	—	8+	Pneumonia, serum, epinephrine	Temperature 102 F.; pulse 140, weak and thready; blood pressure 100/64; sweating profuse; apex beat inaudible	Lobar pneumonia
Arterio- sclerosis	—	3½	22 mo.	22 mo.; 180/110	72	Hematemesis, erythrocyte count 2,540,000	Blood pressure, 80/60; skin cold and clammy; patient weak and irrational; pulse 140; temperature 97 F.; nonprotein nitro- gen 87 mg.	Bleeding gastric ulcer
Arterio- sclerosis, hyper- tension	—	—	2 yr.	2 yr.	72	Vomiting 3 weeks; phenobarbital 10 days; acidosis; blood sugar 672 mg.; carbon dioxide- combining power 22 vol. per cent	Coma and restlessness 7 days before death; blood pressure 100/70 (previously elevated); dehydration	Diabetic coma
Arterio- sclerosis	—	—	—	— 120/76	30	Postoperative peritonitis	Cold, clammy skin; col- lapse, coma; rapid, thready pulse of 140; blood pressure 90/70; temperature 103 F.	Carcinoma of the rectum
Arterio- sclerosis; hyper- tension	—	6	2 mo.	22 yr.; 200/120	+	Pulmonary infarct 4 hr. +	Skin cold and clammy; blood pressure and pulse not obtainable; sweating profuse	Bronchopneumonia; congestive heart failure
Hyper- tension; rheu- matic heart disease	MS MI	11	11 yr.	12 yr.; 180/100- 260/150	24	Auricular flutter (blood pressure 374/187) to auricular fibrillation	Acute collapse with dysp- nea; fall in blood pres- sure from 250/150 to 140/90; distant, poor heart sounds	Congestive failure; paroxysmal auri- cular flutter and fibrillation
Arterio- sclerosis	AS	—	—	—	288	Acute myocardial infarction	Collapse; precordial pain; pallor, dyspnea, cold clammy sweat; blood pres- sure 132/96 12 days before death; bronchopneumonia; nonprotein nitrogen 206 to 288 mg.; carbon dioxide- combining power, 33 vol. %; coma; blood pressure 80/50; pulse 120 for last 5 days	Acute myocardial infarction
Arterio- sclerosis	—	—	—	—	18	Acute myocardial infarction, epinephrine	Sudden substernal pain; dyspnea, pallor, cold sweat; blood pressure 95/60	Acute myocardial infarction

erythrocyte count of 2,500,000, occurred, resulting in shock. Examination revealed a cold clammy skin, a pulse of 140, a temperature of 97 F. and a nonprotein nitrogen content of the blood of 87 mg. per hundred cubic centimeters. Recurrent hemorrhages and persistent shock continued for three days, until death.

Necropsy.—A gastric ulcer with a patent ulcerated artery was observed.

In the heart there was much diffuse fibrosis, particularly in the posterior part of the left ventricle and the interventricular septum, near the base. In one area,

4 cm. in diameter, was an old infarct with complete replacement of muscle by fibrous tissue. There were no recent infarcts. The valves were normal.

The coronary arteries are diagrammed in figure 2.

CASE 3.—Clinical Data.—A woman 69 years of age had had arterial hypertension and diabetes mellitus for two years, but there was no history of angina pectoris. The patient was in diabetic coma for seven days before death. Five days before death, examination in the hospital showed characteristic evidence of diabetic coma, with blood sugar values of 672 mg. and a carbon dioxide-combining power of 22 volumes per hundred cubic centimeters. The blood pressure was 100 systolic and 70 diastolic. Paroxysmal auricular fibrillation was present on admission. The patient improved somewhat but remained comatose for forty-eight hours after admission. She continued to show elevated blood sugar values and on the evening before death experienced severe substernal pain. Tachycardia, a

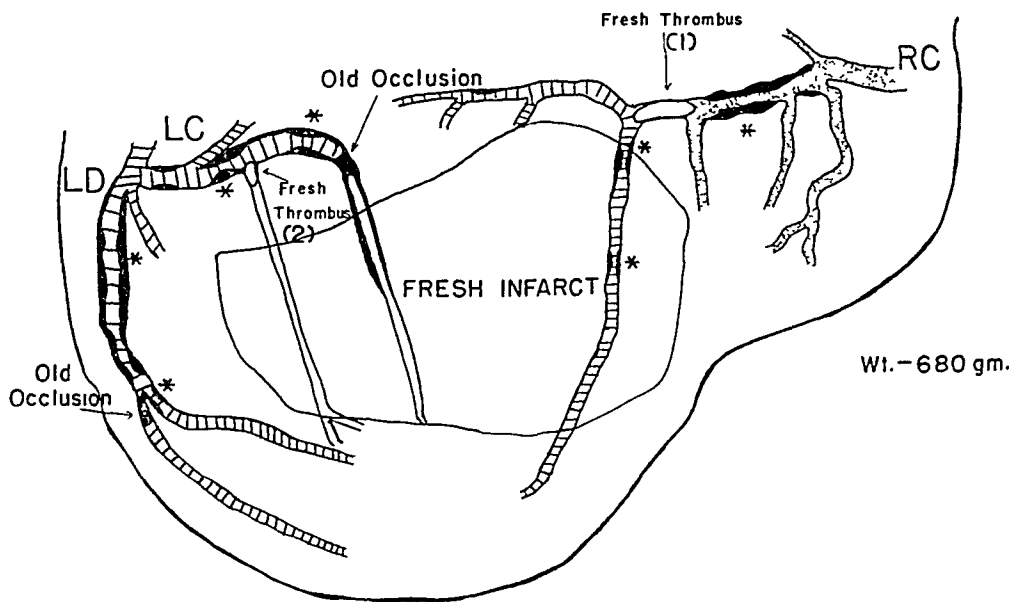


Fig. 3 (case 3).—Fresh adherent thrombi in (1) right coronary artery and (2) branch of left circumflex coronary artery.

blood pressure of 80 systolic and 60 diastolic and other evidences of shock persisted until death, five and a half hours later.

Necropsy.—A large, fresh infarct covered by fibrinous epicardial exudate involved the left ventricle posteriorly and extended well over into the right ventricle. There were slight patchy fibrosis throughout the left ventricle and greatly increased fibrosis in the interventricular septum, visible both grossly and microscopically. The infarcted area revealed extensive fresh myocardial necrosis and acute inflammatory reaction.

The coronary arteries are diagrammed in figure 3.

CASE 4.—Clinical Data.—A man 62 years old was admitted to the hospital nineteen days before death because of a perirectal abscess secondary to carcinoma of the rectum. There was no past history of dyspnea or pain in the chest. The blood pressure was 120 systolic and 76 diastolic. After a colostomy the patient suddenly became cold, clammy and semicomatose; the pulse became rapid and

thready, with a rate of 140 per minute, and the blood pressure fell. Generalized peritonitis, necrosis of the wound and bronchopneumonia developed, and the patient died the following day.

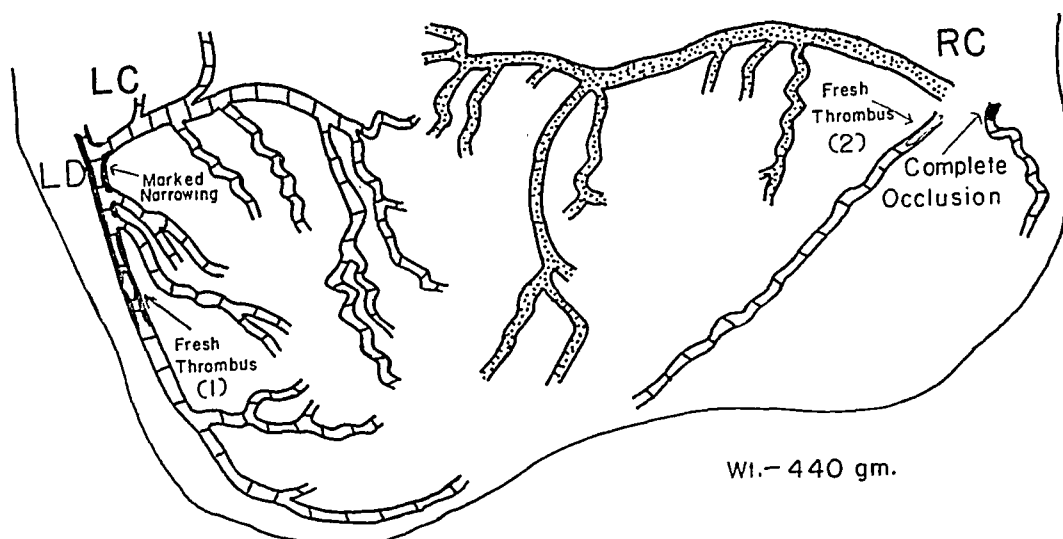


Fig. 4 (case 4).—Fresh adherent thrombi in (1) left anterior descending coronary artery and (2) branch of right coronary artery.

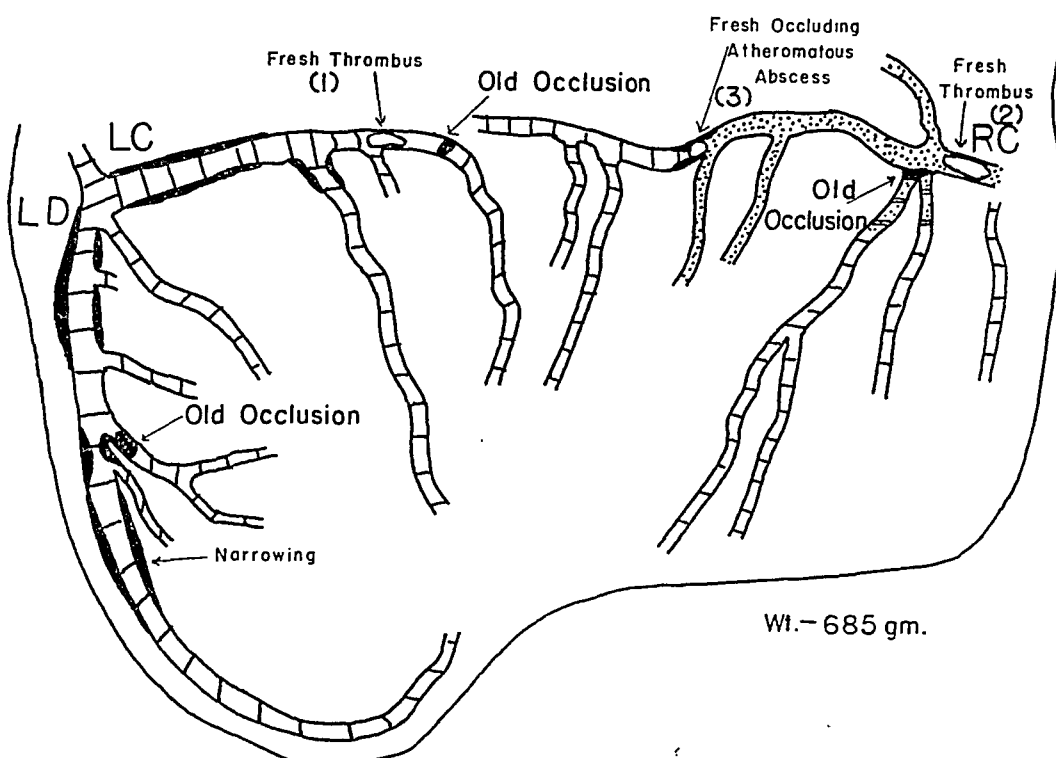


Fig. 5 (case 5).—Fresh adherent thrombi in (1) left circumflex and (2) right coronary arteries and (3) fresh occluding atheromatous abscess in right coronary artery.

Necropsy.—In the heart there were no old or recent infarcts, and the myocardium showed no fibrosis, grossly or microscopically. The valves were essentially normal.

The coronary arteries are diagramed in figure 4.

CASE 5.—*Clinical Data.*—A man 59 years of age, with chronic nephritis and angina pectoris for six years and arterial hypertension for twenty years, had had two episodes of severe, prolonged cardiac pain twelve and seven months, respectively, before death. The last admission to the hospital, five weeks before death, was for treatment of increasing congestive failure, resulting in general anasarca. The patient failed to respond satisfactorily to therapy, showing varying degrees of congestive failure and evidences of bronchopneumonia and azotemia; several decubital ulcers developed. The urine uniformly contained a slight to a pronounced trace of albumin, many white blood cells and occasional granular and hyaline casts; the nonprotein nitrogen content of the blood varied from 51 to 105 mg. per hundred cubic centimeters. During the four hours before death he appeared ashen, had cold clammy skin and complained of precordial pain. The blood pressure was not obtainable.

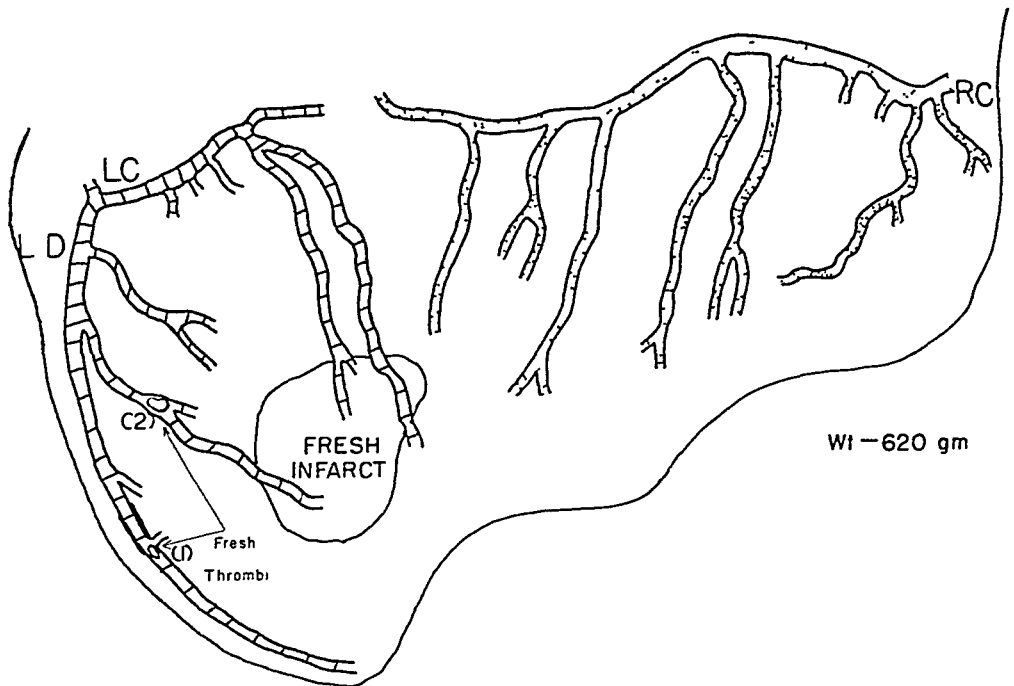


Fig. 6 (case 6).—Fresh adherent thrombi in (1) left anterior descending coronary artery and (2) branch of left anterior descending coronary artery.

Necropsy.—A fresh pulmonary embolus and acute pulmonary infarction were found.

Diffuse arterial and arteriolar nephrosclerosis was evident in the kidneys

In the heart both ventricles were markedly hypertrophied and dilated; the left contained many small scattered areas of fibrosis, but there were no old infarcts. Although the left ventricle posteriorly appeared dusky and bluish, no areas of acute degeneration were found on microscopic examination.

The coronary arteries are diagrammed in figure 5.

CASE 6.—*Clinical Data.*—A man 68 years of age was admitted to the hospital eight days before death because of cardiac pain and evidences of congestive failure. Arterial hypertension, with a pressure of 180 systolic and 110 diastolic to 260 systolic and 150 diastolic, had been present for twelve years, and angina pectoris and congestive failure, for eleven years. Physical examination showed evidence

of moderate congestive failure, cardiac enlargement and the signs of mitral stenosis and insufficiency. For a period of twenty-four hours following admission the characteristic signs of shock and acute pulmonary edema were present associated with auricular flutter, the auricular rate being 374 and the ventricular rate 187. Digitalis converted the flutter to auricular fibrillation. Despite this change, the congestive failure increased progressively, shock continued and the patient died eight days after admission.

Necropsy.—The left ventricle was hypertrophied. Along the lateral border of the left ventricle, near the obtuse margin, there was grossly visible an ill defined area of softening with pinkish gray discoloration of the myocardium. Microscopic evidence of fresh myocardial necrosis was seen. There were no other areas of old or fresh infarction and no diffuse myocardial fibrosis. The mitral valve was stenosed and calcified. The other valves were normal.

The coronary arteries are diagrammed in figure 6.

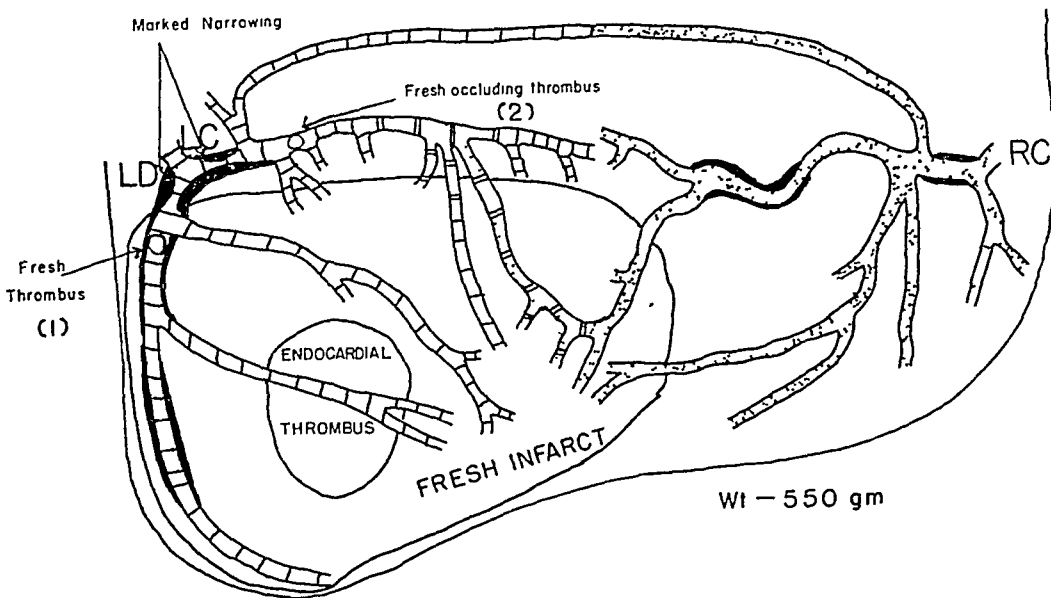


Fig. 7 (case 7).—Fresh adherent thrombi in (1) left anterior descending and (2) left circumflex coronary arteries.

CASE 7.—Clinical Data.—A man 69 years of age had never had any symptoms of congestive failure or of angina pectoris. Twelve days before death he entered the hospital in collapse, seven hours after the sudden onset of persistent substernal pain. Physical examination showed a pale, cold, clammy skin, dyspnea, a blood pressure of 132 systolic and 96 diastolic and tachycardia, with a rate of 100 per minute. Evidences of circulatory collapse persisted, but to a lesser extent, until five days before death, when signs of bronchopneumonia developed and the patient became semicomatose. The nonprotein nitrogen of the blood varied from 156 to 228 mg. per hundred cubic centimeters. The carbon dioxide-combining power was 33 to 38 volumes per cent. The pulse was not obtainable, and the blood pressure was 80 systolic and 50 diastolic during the forty-eight hours before death.

Necropsy.—There was extensive polycystic disease of the kidneys, involving two thirds of one kidney and three fourths of the other. The remaining kidney tissue showed arteriolar sclerosis.

In the heart there were a large, fresh infarct involving the entire left ventricle and the interventricular septum and a large, partly organized endocardial thrombus

at the apex of the left ventricle. Scattered areas of fibrosis were present in the left ventricle posteriorly near the septum. Both the aortic and the mitral valves were calcified, the aortic valve being stenosed.

The coronary arteries are diagrammed in figure 7.

CASE 8.—Clinical Data.—A man 65 years of age entered the hospital because of severe precordial pain, of four hours' duration. There was no history of angina pectoris or of congestive failure. His physician had administered epinephrine to combat shock, but severe pain and collapse continued. Examination showed a cold clammy skin, ashen cyanosis, pulmonary edema and a blood pressure of 95 systolic and 60 diastolic. Shortly after the patient's admission his pulse and blood pressure were unobtainable, and he died eighteen hours after the onset of the continuous precordial pain and shock.

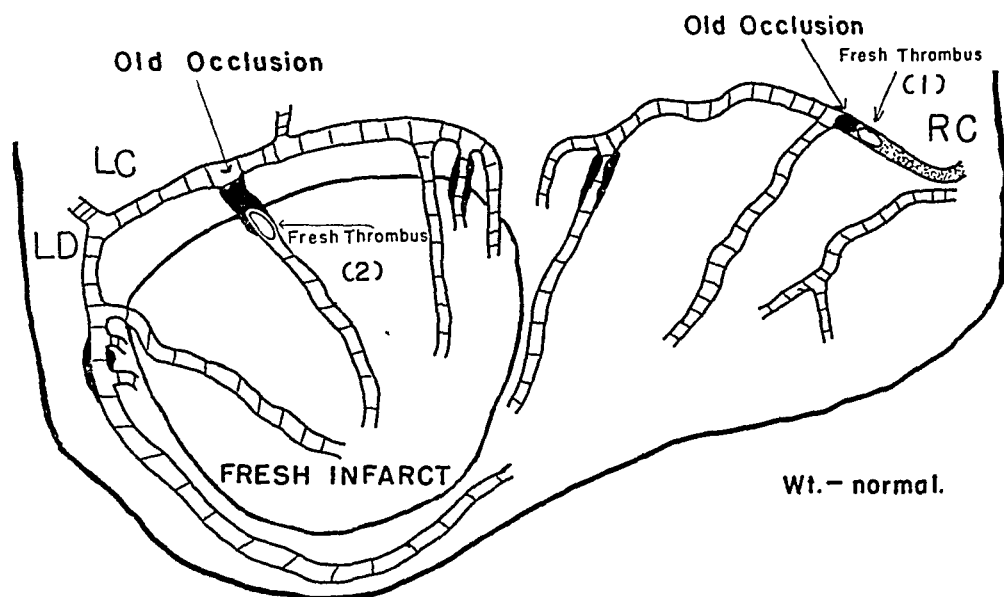


Fig. 8 (case 8).—Fresh adherent thrombi in (1) right coronary artery and (2) branch of left circumflex coronary artery.

Necropsy.—There was no fibrosis or old infarction in the heart. A large, fresh infarct was found involving almost the entire left ventricle.

The coronary arteries are diagrammed in figure 8.

COMMENT

Cases of Multiple Fresh Thrombotic Occlusions.—In each of the cases of multiple fresh coronary thrombotic occlusions, the patient had been in collapse for periods varying from eight to two hundred and eighty-eight hours. Such multiple thrombi have not been observed to date in any case of our series in which peripheral vasomotor collapse was absent. The thrombi in the coronary arteries were clearly formed ante mortem and in each instance were adherent to the vessel walls. The technic utilized in this study is especially suitable for the disclosure of such occlusions, since it includes the inspection of the contents of the three main coronary arteries and all main branches throughout their entire

extent. This readily displays all coronary occlusions, both fresh thrombotic and old healed. An occlusion was interpreted as fresh when it was considered of a duration equal to or less than the terminal illness. Various stages of organization were found in the adherent thrombi when they were examined microscopically.

The fact that the multiple fresh coronary occlusions were found in widely different parts of the coronary arterial system indicates that they were precipitated by conditions affecting the heart generally, rather than by factors restricted to one localized area of the coronary arterial tree.

Certain characteristics commonly found in these cases may be listed as follows:

1. Age: All patients were elderly, ranging in age from 59 to 69 years and averaging 65 years (table 1).

2. Clinical Evidences of Coronary Arterial Disease: Evidences of such disease as angina pectoris or congestive failure had been present in 5 of the 8 cases for two to eleven years; in 4 cases there had been arterial hypertension. Thus the patients in 5 of the 8 cases were known to have heart disease prior to the onset of shock.

3. Pathologic Evidence of Coronary Arterial Disease with Marked Narrowing or Old Occlusion: Such evidence was present in the heart in all but 1 case. In the exceptional instance (case 6), with the least coronary arteriosclerosis of any heart in the series, the patient had had angina pectoris and congestive failure for eleven years, due largely to the increased cardiac work secondary to mitral stenosis and insufficiency, and arterial hypertension. In every heart of this series collateral circulatory pathways were demonstrable distal to the old or the fresh occlusions. As pointed out in previous communications, collateral circulation generally has been found to develop only when and where it is needed, in regions where it is plausible to assume relative coronary insufficiency.¹ Additional pathologic evidence indicative of diminished coronary blood flow is afforded by the presence of moderate to marked myocardial fibrosis in 6 of the 8 hearts and healed myocardial infarcts in 2 (table 1).

4. Antecedent Shock: It is commonly recognized that shock constitutes one of the most prominent clinical features of acute coronary arterial thrombosis. This series, however, suggests that the reverse sequence commonly occurs in cases of multiple fresh occlusions, i. e., shock due to noncardiac conditions, or occurring occasionally as a consequence of congestive failure, may secondarily precipitate multiple fresh occlusions.

In 6 of the 8 cases (1, 2, 3, 4, 5 and 6) shock was caused by conditions other than myocardial infarction. In these cases shock was due primarily to the following clinical conditions: case 1, lobar pneumonia; case 2, massive hematemesis from a gastric ulcer; case 3, diabetic coma;

case 4, carcinoma of the rectum; case 5, pulmonary infarction, bronchopneumonia, congestive failure and uremia, and case 6, paroxysmal auricular flutter with a ventricular rate of 187 and congestive failure.

Special comment on several of these cases is warranted. In case 3 the patient was in diabetic coma from the seventh to the third day before death. Some clinical improvement then occurred but was interrupted by the onset of persistent cardiac pain and peripheral vasomotor collapse, terminating in death five and a half hours later. The multiple thrombi found post mortem were partly organized, and the myocardial necrosis was too far advanced to be compatible with a duration of but five and a half hours. These changes were probably initiated during the period of extreme diabetic coma, which existed from the seventh to the third day before death. In case 5 congestive failure persisted, though to a somewhat lessened degree, after admission, but the patient's clinical condition became progressively more precarious because of nitrogen retention, marked secondary anemia, development of two decubital ulcers and continued evidences of pulmonary infection, with a temperature mounting almost daily to 102 F. and a leukocyte count varying from 7,700 to 28,800. The patient had been in a debilitated and precarious condition for several weeks, but complained of precordial discomfort and became ashen and covered with a cold clammy perspiration only four hours before death. The thrombus of the right coronary artery was obviously more recent than that found in the left circumflex artery; the latter was organized. In case 6 auricular flutter with a ventricular rate of 187 appeared eight days before death; with it collapse occurred and persisted for twenty-four hours. Congestive failure increased, and the patient died eight days later, although the ventricular rate had been controlled. Both the severe terminal congestive failure and the shock attendant on auricular flutter were contributory factors in producing multiple occlusions in this instance.

In only 2 cases (7 and 8) did the onset of the characteristic syndrome of acute myocardial infarction lead to hospitalization. In these cases the shock of acute myocardial infarction due to acute coronary thrombosis may well have been responsible for the occurrence of the other fresh thromboses. Thus, the patient in case 7 showed improvement for several days after the initial attack, only to suffer a second episode of shock, terminating in death. The heart showed two coronary arterial thrombi; the one in the left circumflex artery was very fresh, and the other in the left descending artery, much older. In case 8 the two fresh thrombi, each in different arteries, were found in blind pockets proximal to old calcified occlusions. They did not block any dissectable branches of the main coronary arteries and presumably were a consequence rather than a cause of the shock. In this instance shock was evidently due to acute extensive myocardial infarction.

The clinical and pathologic observations on these patients suggest that the fresh multiple thrombi were the result of several different sequences of events. In some instances all of the multiple fresh thrombi probably occurred during the period of shock immediately preceding death. In other instances the degree of organization of the thrombus indicated that it was produced during an earlier period of shock, preceding the terminal events by several days. The finding of both a partially organized and a very fresh coronary arterial thrombus in several hearts suggests that one or more arterial thrombi occurred during each period of shock.

According to the observations in cases 3, 5, 6, 7 and 8, arterial thrombi may be initiated some days before death, and only later, when they are more fully developed, do the characteristic evidences of myocardial infarction appear. Feil⁴ and Sampson and Eliaser⁵ have commented on the frequency with which premonitory symptoms occur hours or days preceding the abrupt onset of acute myocardial infarction. One of them (4) stated: "A gradually forming thrombus in a stenosed coronary artery appears to be the most probable explanation for the occurrence of the preliminary pain." In the cases of this series, premonitory symptoms were not frequent, owing perhaps to the associated shock and clouding of consciousness following medication. Master and his associates⁶ have previously noted that the diagnosis of "coronary artery occlusion" is made with difficulty postoperatively because in only two fifths of their cases was pain experienced. They stated: "This disparity may be accounted for, in part, by the liberal use of narcotics and sedatives after operation." It is of interest in this connection that multiple acute thrombi were present in 1 of their 19 patients examined post mortem.

Cases of Single Fresh Thrombotic Occlusion.—Several of the non-cardiac conditions which led to shock and the precipitation of multiple thrombi in our patients have been cited by various authors as of importance in the precipitation of a *single* coronary occlusion. Saphir, Priest, Hamburger and Katz⁷; Master, Dack and Jaffe,⁶ and others⁸ have

4. Feil, H.: Preliminary Pain in Coronary Thrombosis. *Am. J. M. Sc.* **193**:42, 1937.

5. Sampson, J. J., and Eliaser, M., Jr.: The Diagnosis of Impending Acute Coronary Artery Occlusion, *Am. Heart J.* **13**:675, 1937.

6. Master, A. M.; Dack, S., and Jaffe, H. L.: Postoperative Coronary Artery Occlusion, *J. A. M. A.* **110**:1415 (April 30) 1938.

7. Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, *Am. Heart J.* **10**:567, 1935.

8. Fishberg, A. M.: *Heart Failure*, Philadelphia, Lea & Febiger, 1937, p. 655. Fitz-Hugh, T., Jr., and Wolferth, C. C.: Cardiac Improvement Following Gallbladder Surgery, *Ann. Surg.* **101**:478, 1935. Harrison, T. R.: *Failure of the Circulation*, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

stressed the frequency with which coronary arterial occlusion occurs postoperatively. Others⁹ have suggested that a fall in blood pressure following glyceryl trinitrate therapy and under other conditions leads to coronary occlusion. Similarly, the significance, as precipitating factors, of massive hemorrhage, infection, diabetic coma and hypoglycemia, in all of which shock is common, has been noted.¹⁰ It also has been pointed out that congestive failure may lead to shock and initiate coronary arterial thrombosis.^{10a}

Among the 350 cases we have studied, there were, in addition to the 8 instances of multiple fresh coronary thrombosis just discussed, 22 others in which a single fresh coronary arterial thrombus occurred. The incidence in these 22 cases of the precipitating factors just enumerated is shown in table 2. The coronary episode was an incidental or terminal event, secondary to shock following noncardiac disorders or congestive failure in 10, or almost half, of these cases. This analysis of a relatively

TABLE 2.—*Precipitating Factors in Twenty-Two Cases of Single Acute Coronary Thrombus*

	Number of Cases
A. Cases without evident precipitating factors.....	12
B. Cases associated with other clinical conditions.....	10
Precipitating factor	
Uremia.....	3
Congestive failure.....	2
Infarction.....	1
Diabetic coma.....	3
Postoperative cholemia.....	1

small but representative group of cases of hospitalized patients confirms the importance of such conditions in the precipitation of fresh coronary arterial occlusion. It emphasizes the significance of the correlation between multiple fresh occlusions and shock. Numerous factors unquestionably operate in each instance, their relative importance varying from case to case. Dehydration, diminished blood volume, oxygen unsatura-

9. Luten, D.: *Contributory Factors in Coronary Occlusion*, Am. Heart J. **7**: 36, 1931. Sprague, H. B., and White, P. D.: *Nitroglycerine Collapse: A Potential Danger in Therapy*, M. Clin. North America **16**:895, 1933. Pepper, O. H.: *Hypotension—Growing Appreciation of Its Importance*, Northwest Med. **34**:325, 1935. Proger, S. H., and Ayman, D.: *Harmful Effects of Nitroglycerin, with Special Reference to Coronary Thrombosis*, Am. J. M. Sc. **184**:480, 1932.

10. (a) Bean, W. B.: *Infarction of the Heart: A Morphological and Clinical Appraisal of Three Hundred Cases*; I. Predisposing and Precipitating Conditions, Am. Heart J. **14**:684, 1937; II. Symptomatology of Acute Attack, Ann. Int. Med. **11**:2086, 1938; III. Clinical Course and Morphological Findings, *ibid.* **12**:71, 1938. (b) Blotner, H.: *Coronary Disease in Diabetes Mellitus*, New England J. Med. **203**:709, 1930. (c) Enklewitz, M.: *Diabetes and Coronary Thrombosis*, Am. Heart J. **9**:386, 1934.

tion of the arterial blood, impaired nutrition and increased permeability of the blood vessel walls due to toxemia, and other physical and chemical changes in the blood are some of the conditions associated with stasis and lowered blood pressure which must be considered etiologically significant. The fact that arterial hypertension and valvular disease were also frequently present in these cases suggests that increased work of the heart likewise plays a predisposing role. Previous communications¹ have emphasized the importance of the speed with which closure of the coronary arteries occurs and the factor of safety provided by the development of an anastomotic circulation. A single, suddenly formed thrombus throws an abrupt, severe strain on an already reduced cardiac blood supply; all the more disastrous to the coronary circulation must be the sudden deposition of multiple thrombi.

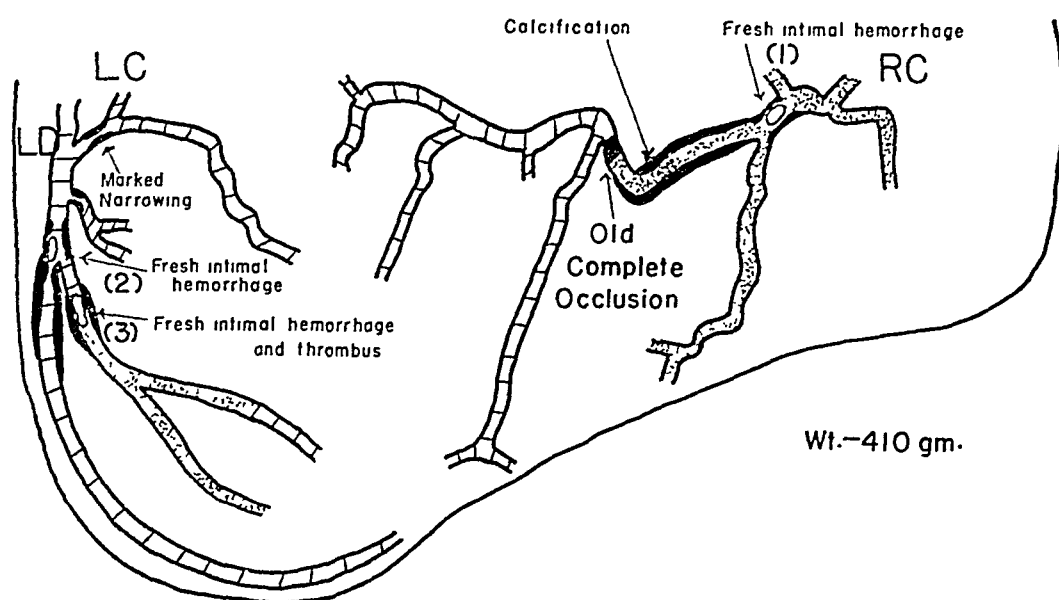


Fig. 9.—Coronary arterial tree showing fresh intimal hemorrhages in (1) right coronary and (2) left anterior arteries and (3) fresh thrombosis at site of intimal hemorrhages in primary branch of left anterior descending artery.

Occlusion by Mechanisms Other Than Thrombosis.—The fresh occlusions in the coronary arteries in the 30 cases listed in tables 1 and 2 were due to the deposition of fresh thrombi. In 19 other cases both single and multiple coronary arterial occlusions were produced by other mechanisms, namely, ulceration of atheromatous abscesses and fresh intimal hemorrhages into an atheromatous plaque.

In 3 of these 19 cases multiple fresh nonthrombotic occlusions were found. In the first case (fig. 9) shock was presumably precipitated by the firmly adherent thrombus in the primary branch of the left anterior descending artery. Two other fresh intimal hemorrhages, in the left anterior descending and the right coronary artery, may have occurred

coincidentally or subsequently, secondary to the necrotizing myocarditis with shock attendant on the fresh thrombosis. In the second case the patient suffered a cerebral vascular accident with hemiplegia and remained comatose and in collapse until he died, four days later. In his heart (fig. 10) no fresh thrombi were found, but two intimal hemorrhages and a ruptured atheromatous abscess were observed. In a third case the patient had entered the hospital four weeks before death because of congestive failure, which responded satisfactorily to treatment. After all evidences of congestive failure had disappeared, rectal hemorrhage leading to shock occurred. Two fresh intimal hemorrhages and fresh infarction of the left ventricle were found in the heart (fig. 11).

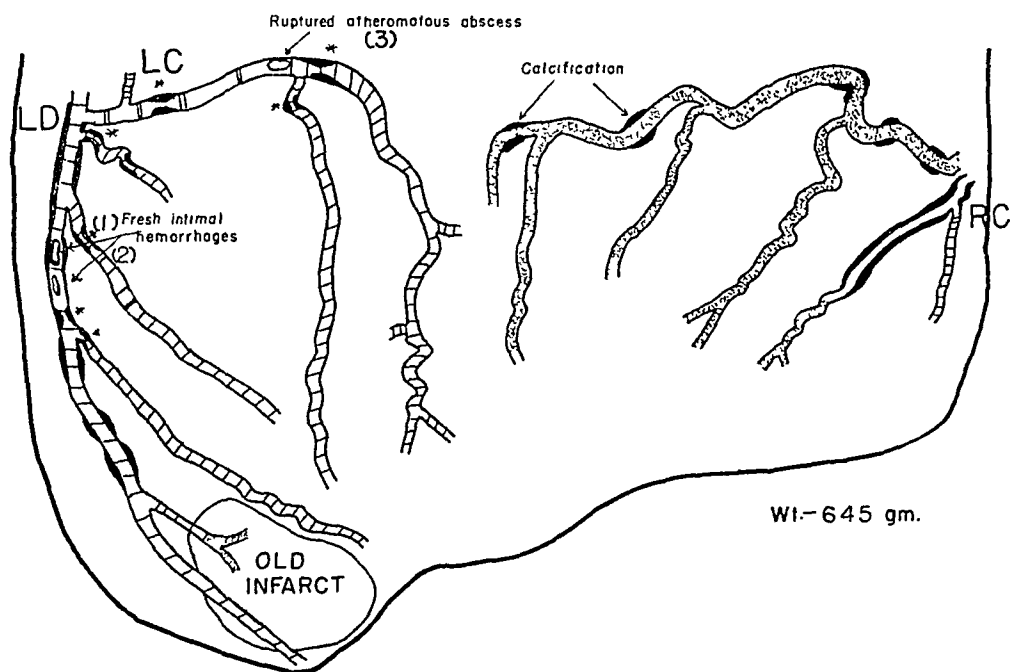


Fig. 10.—Coronary arterial tree showing (1 and 2) fresh intimal hemorrhages in left anterior descending artery and (3) ruptured atheromatous abscess in left circumflex artery.

Thus, in 2 of the 3 cases of multiple nonthrombotic coronary occlusion the patient died in shock of noncardiac origin. Also, of the remaining 16 cases of single nonthrombotic occlusion, shock was precipitated in 10 by primary disease of noncardiac origin, such as post-operative state, uremia, infection, hemorrhage and diabetic coma.

Types of Fresh Lesions Present in Coronary Arteries.—Multiple fresh occlusions and narrowings of the coronary arteries in all cases were due to: (1) deposition of fresh thrombi on arteriosclerotic plaques; (2) ulceration of atheromatous abscesses, or (3) fresh, intimal hemorrhages into an atheromatous plaque. In 3 instances (figs. 5, 9 and 10) two of these mechanisms were operative simultaneously. The finding of these

three types of occlusion intermingled in the hearts in this series of cases suggests that the mechanisms of their production may be similar.

That a coronary thrombus may arise from the base of a ruptured intimal hemorrhage¹¹ or on the site of a ruptured atheromatous abscess¹² and that various influences predispose to the rupture of intimal capillaries and intramural hemorrhage have been discussed by several authors. The implication of this study is that the changes produced in the coronary arteries by shock, that is, impaired nutrition, increased permeability of the vessel wall, stasis and lowered arterial tension, favor the formation of all three types of narrowing and occlusion. These considerations are not contrary to the possibility suggested by Paterson¹³ that, with exertion or excitement, similar lesions may be produced

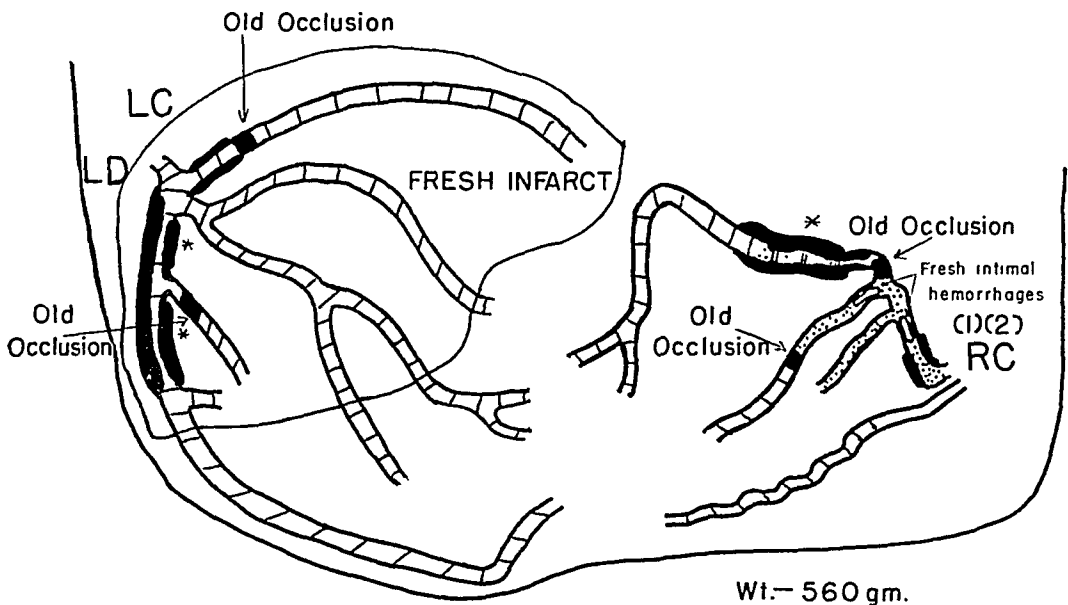


Fig. 11.—Coronary arterial tree showing fresh infarction and fresh intimal hemorrhages in (1) right coronary artery and (2) primary branch of right coronary artery.

during transitory rises of blood pressure by the relative anoxia or other factors prevailing under such circumstances.

11. Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, *Arch. Path.* **22**:313 (Sept.) 1936. Wartman, W. B.: Occlusion of the Coronary Arteries by Hemorrhage into Their Walls, *Am. Heart J.* **15**:459, 1938. Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, *Arch. Path.* **25**:474 (April) 1938. Horn and Finkelstein.^{2c}

12. Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary) Atherosclerosis, *Arch. Path.* **17**:453 (April) 1934; *Pathology of Coronary Sclerosis*, *Am. Heart J.* **10**:328, 1935.

13. Paterson, J. C.: Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombi, *J. A. M. A.* **112**:895 (March 11) 1939.

SUMMARY

In a series of 350 cases, 11 were found in which the heart showed multiple fresh coronary arterial occlusions, all occurring in the presence of shock. Of these, 8 were instances of multiple thrombosis and 3 were instances of multiple fresh nonthrombotic occlusions. The shock was due to conditions other than myocardial infarction in 8 of these 11 cases. In all, the patients were elderly and gave marked clinical and pathologic evidence of coronary disease. In addition, a single fresh coronary occlusion was found in 38 cases, in 22 of which it was due to a thrombotic and in 16 to a nonthrombotic mechanism. Shock due to noncardiac causes or congestive failure was present in approximately half of these cases.

CONCLUSIONS

Shock, no matter how produced, may lead in elderly patients, particularly in those showing evidence of coronary arteriosclerosis, to the development not only of single, but often of multiple, fresh coronary arterial occlusions. To avert such disastrous complications, the manifestations of shock, such as lowering of blood pressure, tachycardia and dehydration, must be combated with particular vigor in these patients.

DIFFERENTIATION OF INTRAHEPATIC AND EXTRAHEPATIC JAUNDICE

RESPONSE OF THE PLASMA PROTHROMBIN TO INTRAMUSCULAR
INJECTION OF MENADIONE (2-METHYL-1, 4-NAPHTHOQUINONE)
AS A DIAGNOSTIC AID

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AND

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While in the majority of cases in which the patient enters the hospital with jaundice as the presenting complaint the cause can be diagnosed on the basis of the history and physical examination, there remains a certain group in which a decision as to whether the jaundice is of intrahepatic or extrahepatic origin cannot be made with certainty. In these cases laboratory tests must often be looked to for aid in the differential diagnosis.

During the past ten years a wide variety of tests and technics have been devised as useful aids in the differential diagnosis of intrahepatic (catarrhal jaundice, hepatitis, cirrhosis of the liver and hepatic abscess) and extrahepatic jaundice (occlusion within or pressure from without the common bile duct). The use of these tests is predicated on the fact that jaundice of intrahepatic origin is more commonly associated with damage to the liver than is that due to stone or other extrahepatic lesion.

Considerable literature has accumulated concerning the value of such tests, and it may be well to review some of the more important contributions.

REVIEW OF LITERATURE

I. *Galactose Tolerance Test*.—Shay and Schloss¹ in 1932 advocated the use of this test for the differential diagnosis of painless jaundice but did not state the number of cases in which it was used or the per-

E. R. Squibb & Sons supplied us with menadione (2-methyl-1,4-naphthoquinone).

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This study was carried out under grants from the John and Mary R. Markle Foundation and the Dula Foundation.

1. Shay, H., and Schloss, E.: Painless Jaundice: Its Differential Diagnosis by Galactose Tolerance Test, J. A. M. A. **98**:1433 (April 23) 1932.

centage of error of the test. In 1934 Schiff and Senior² reported remarkable success with this test in distinguishing between intrahepatic and extrahepatic jaundice. The test was positive (output of galactose exceeding 3 Gm.) in 49 out of 50 cases of catarrhal jaundice and 14 out of 15 cases of acute toxic hepatitis. A negative test (output of less than 3 Gm.) was obtained in 20 out of 20 cases of obstructive jaundice. In contrast to these authors, Banks, Sprague and Snell³ suggested in 1933 that the galactose tolerance test was not entirely reliable in the differential diagnosis of these two types of jaundice, since in a group of cases of acute and subacute intrahepatic jaundice the test was negative (less than 3 Gm.) in 3 out of 18 cases. In the cases of chronic jaundice of intrahepatic origin the test was negative in 11 out of 13. However, the most striking observation was a positive test (3 Gm. or more) in 14 out of 30 cases of jaundice due to malignant disease outside the liver (carcinoma of the ampulla of Vater, head of the pancreas and common or hepatic ducts). In their group of 38 cases of non-malignant obstructive jaundice the galactose tolerance test was positive in 12.

White⁴ reported his experience with the galactose tolerance test in 1937 and noted that the test was positive in 10 out of 17 cases of catarrhal jaundice, in 15 out of 17 cases of toxic hepatitis and in 1 out of 12 cases of obstructive jaundice. This report is slightly more optimistic than that of Banks, Sprague and Snell³ concerning the value of the galactose tolerance test, but still shows a significant degree of overlapping, particularly when the test was negative.

We have employed the galactose tolerance test in 12 cases of jaundice and have found that the test was positive (more than 3 Gm. excreted) in 6 out of 7 cases of intrahepatic jaundice but was also positive in 2 out of 5 cases of extrahepatic jaundice (tables 1 and 2).

II. *Cholesterol and Cholesterol Ester*.—Epstein and Greenspan⁵ in 1936 found that in obstructive jaundice the total cholesterol and the cholesterol ester both paralleled the increase of bilirubin in the blood, whereas in parenchymatous degeneration of the liver (catarrhal jaundice,

2. Schiff, L., and Senior, F. A.: A Study of One Hundred Cases of Jaundice, with Particular Reference to Galactose Tolerance, *J. A. M. A.* **103**:1924 (Dec. 22) 1934.

3. Banks, B. M.; Sprague, P. H., and Snell, A. M.: Clinical Evaluation of Galactose Tolerance Test, *J. A. M. A.* **100**:1987 (June 24) 1933.

4. White, F. W.: Galactose Tolerance and Urobilinogen Tests in Differential Diagnosis of Painless Jaundice, *Am. J. Digest. Dis. & Nutrition* **4**:315 (July) 1937.

5. Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of Cholesterol Partition of Blood Plasma in Hepatic and in Biliary Diseases, *Arch. Int. Med.* **58**:860 (Nov.) 1936.

toxic hepatitis, acute yellow atrophy, etc.) the cholesterol was normal or low, while the cholesterol ester was extremely low—at times being present only in traces. Ottenberg and Colp⁶ presented the following data on 84 cases of jaundice: Of 26 cases of jaundice due to stone the cholesterol of the blood was high in 19 and low in 6, while the cholesterol ester was low in 14 out of 26 cases. In the group of cases

TABLE 1.—*Extrahepatic Jaundice; Comparative Accuracy of Tests*

Type of Test	Authors	Total Number of Cases	Cases with Normal Response	Per Cent Correct
I. Galactose tolerance	Schiff and Senior.....	20	20	100
	Banks, Sprague and Snell.....	63	42	60
	White.....	12	11	92
	Lord and Andrus.....	5	3	60
II. Serum phosphatase	Rothman, Meranze and Meranze...	29	25	86
	Cantarow and Nelson.....	31	21	68
III. Hippuric acid	Quick.....	3	2	67
	Snell and Plunkett.....	12	2	17
	Lord and Andrus.....	3	3	100
IV. Flocculation	Hanger.....	25	25	100
V. Response to plasma prothrombin to menadione	Lord and Andrus.....	18	18	100

TABLE 2.—*Intrahepatic Jaundice; Comparative Accuracy of Tests*

Type of Test	Authors	Total Number of Cases	Cases with Abnormal Response	Per Cent Correct
I. Galactose tolerance	Schiff and Senior.....	65	63	97
	Banks, Sprague and Snell.....	31	17	55
	White.....	34	25	74
	Lord and Andrus.....	7	6	86
II. Serum phosphatase	Rothman, Meranze and Meranze...	24	18	75
	Cantarow and Nelson.....	22	12	55
	Lord and Andrus.....	2	1	50
III. Hippuric acid	Quick.....	13	12	92
	Snell and Plunkett.....	6	4	67
	Lord and Andrus.....	6	4	67
IV. Flocculation	Hanger.....	38	33	87
V. Response of plasma prothrombin to menadione	Lord and Andrus.....	10	10	100

of jaundice due to carcinoma the cholesterol was high in 14 out of 16, while the ester was low in 5 out of 16. In their third group of 42 cases of hepatitis, the blood cholesterol was high in 12 and low in 17 and the ester was low in 23. From the data it would seem that this test has little value in differentiating jaundice due to stone and that due to hepatitis in any given case. According to their results,

6. Ottenberg, R., and Colp, R.: *Diagnosis of Surgical Jaundice*, New York State J. Med. **37**:1011 (June 1) 1937.

the test would tend to rule out malignant obstruction if the cholesterol was low.

III. *Serum Phosphatase*.—According to their report made in 1936, Rothman, Meranze and Meranze⁷ found this test to be the most useful one for the differential diagnosis of jaundice. They found that a phosphatase value greater than 10 units occurred in 25 out of 29 cases of extrahepatic jaundice, while in 18 out of 24 cases of intrahepatic jaundice the level of blood phosphatase was 10 units or less.

In 1937 Cantarow and Nelson⁸ stated that in their experience there is marked overlapping of the levels of blood phosphatase in obstructive and hepatocellular jaundice and hence that the test has practically no value as a differential diagnostic aid.

In only 2 cases in our present series were serum phosphatase determinations made. In both of these cases the patients had intrahepatic jaundice, and the phosphatase levels were 3.7 and 10.2 Bodansky units, respectively.

IV. *Hippuric Acid Test*.—Quick⁹ in 1936 reported his experience with this test and concluded that it seemed useful in differentiating jaundice due to hepatitis and that arising from stone in the common duct. In 7 out of 7 cases of catarrhal jaundice and in 5 out of 6 cases of hepatitis of known origin the excretion of hippuric acid was significantly reduced. In 1 case of carcinoma of the head of the pancreas with an icteric index of 120, the hippuric acid excretion was only 41 per cent of normal. In 2 cases of obstruction of the common duct due to stones the hippuric acid excretion was 105 and 104 per cent of normal.

Snell and Plunkett¹⁰ in 1936 correlated the results of the hippuric acid test with those of the galactose tolerance and bromsulphalein tests and concluded that the hippuric acid test indicates more accurately the degree of damage to the liver in most cases of jaundice. They added, however, that the test does not differentiate extrahepatic and intrahepatic jaundice. Boyce and McFetridge¹¹ have independently arrived at the

7. Rothman, M. M.; Meranze, D. R., and Meranze, T.: Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice, *Am. J. M. Sc.* **192**:526 (Oct.) 1936.

8. Cantarow, A., and Nelson, J.: Serum Phosphatase in Jaundice, *Arch. Int. Med.* **59**:1045 (June) 1937.

9. Quick, A. J.: Clinical Value of Test for Hippuric Acid in Cases of Disease of Liver, *Arch. Int. Med.* **57**:544 (March) 1936.

10. Snell, A. M., and Plunkett, J. E.: The Hippuric Acid Test for Hepatic Function: Its Relation to Other Tests in General Use, *Am. J. Digest. Dis. & Nutrition* **2**:716 (Feb.) 1936.

11. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test: I. Biliary and Hepatic Disease, *Arch. Surg.* **37**:401 (Sept.) 1938.

same conclusions as Snell and Plunkett concerning the value and limitations of the hippuric acid test.

We have employed the hippuric acid test in the cases of 9 patients. Of 6 cases of intrahepatic jaundice the test was normal in 2, and in all 3 of the cases of jaundice which was extrahepatic in origin results were normal.

V. Flocculation Test.—In 1939 Hanger¹² reported his experience with flocculation of cephalin-cholesterol emulsions by the serums of jaundiced patients. As a differential diagnostic aid this test would seem to be more accurate than any hitherto reported. In 25 cases of extrahepatic jaundice, irrespective of cause, the flocculation reaction was either negative or at the most 1 plus, while in the group of cases of intrahepatic jaundice (hepatitis, catarrhal jaundice and cirrhosis) 33 out of 38 showed a prompt, strong flocculation reaction. Three of the 5 normal reactions occurred in cases of jaundice following the administration of arsphenamine.

Considerable evidence has accumulated during the past three years to indicate that the plasma prothrombin is intimately related to the liver and its normal function. Thus, in 1937 Smith, Warner and Brinkhous¹³ showed that after ninety minutes of deep chloroform anesthesia the plasma prothrombin in the dog fell to less than 5 per cent of normal in forty-eight hours and did not return to normal until six days had elapsed. Warner,¹⁴ in 1938, extirpated approximately two thirds of the liver of the rat and observed a fall in the plasma prothrombin to 35 per cent of normal, accompanied by recovery in two and a half weeks. Warren and Rhoads¹⁵ and Andrus, Lord and Moore¹⁶ independently performed total hepatectomy in the dog and observed a fall in the plasma prothrombin to less than 10 per cent of normal in fourteen hours. The latter authors also noted in animals that the administration of even very large doses of vitamin K failed to alter the curve of fall of the plasma prothrombin after hepatectomy. Clinical studies by Butt, Snell

12. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, *J. Clin. Investigation* **18**:261 (May) 1939.

13. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66**:801 (Dec.) 1937.

14. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, *J. Exper. Med.* **68**:831 (Dec.) 1938.

15. Warren, R., and Rhoads, J. E.: Hepatic Origin of Plasma Prothrombin Observations After Total Hepatectomy in the Dog, *Am. J. M. Sc.* **198**:193 (Aug.) 1939.

16. Andrus, W. DeW.; Lord, J. W., Jr., and Moore, R. A.: Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K, *Surgery* **6**:899 (Dec.) 1939.

and Osterberg,¹⁷ Pohle and Stewart,¹⁸ Brinkhous, Smith and Warner¹⁹ and Andrus and Lord²⁰ have demonstrated that in patients with obvious hepatic damage the level of the plasma prothrombin may fail to be elevated after the administration of vitamin K.

Wilson²¹ was the first to suggest that the level of the plasma prothrombin as determined by the Warner, Brinkhous and Smith²² test might serve as a measure of hepatic function, and he was able to correlate this satisfactorily with the excretion of hippuric acid. It is known, however, that the prothrombin of the plasma may be depressed by such factors as faulty absorption, and it would therefore seem unwise to accept the level alone as a measure of hepatic function.

REPORT OF INVESTIGATION

During the first year of the studies carried out in the New York Hospital we were impressed by the fact that certain patients with hypoprothrombinemia failed to respond satisfactorily to oral vitamin K therapy in the form of klotogen²³ or cerophyl.²⁴ In some of these cases (fig. 1) the hepatic function as determined by the hippuric acid test was normal, while in others there was significant hepatic damage (fig. 2). With the discovery of the synthetic form, now known as menadione (2-methyl-1,4-naphthoquinone)²⁵ and with the introduction of the intramuscular

17. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Pre-Operative and Post-Operative Administration of Vitamin K to Patients Having Jaundice, *J. A. M. A.* **113**:383 (July 29) 1939.

18. Pohle, F. J., and Stewart, J. K.: Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, *J. Clin. Investigation* **19**:365 (March) 1940.

19. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula: Effect of Feeding Bile and Alfalfa (Vitamin K), *Am. J. M. Sc.* **196**:50 (July) 1938.

20. Andrus, W. DeW., and Lord, J. W., Jr.: Correction of Prothrombin Deficiencies by Means of 2-Methyl-1, 4-Naphthoquinone Injected Intramuscularly, *J. A. M. A.* **114**:1336 (April 6) 1940.

21. Wilson, S. G.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, *Proc. Soc. Exper. Biol. & Med.* **41**:559 (June) 1939.

22. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clottings: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667 (Feb.) 1936.

23. A concentrate of vitamin K (menadione) in peanut oil, manufactured by the Abbott Laboratories.

24. A preparation of powdered cereal grasses which contains provitamin A (carotene), vitamin B₁ (thiamine), vitamin C and vitamin G (riboflavin) and is a rich source of vitamin K.

25. Ansbacher, S., and Fernholz, E.: Simple Compounds with Vitamin K Activity, *J. Am. Chem. Soc.* **61**:1024 (July) 1939.

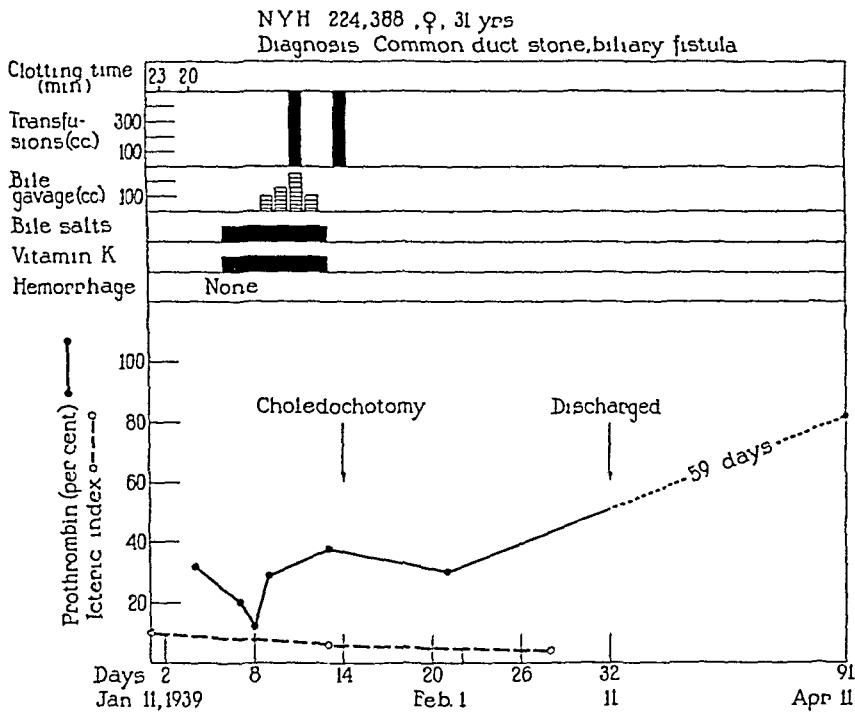


Fig. 1.—Failure of plasma prothrombin to respond to oral vitamin K therapy in a case of normal hepatic function.

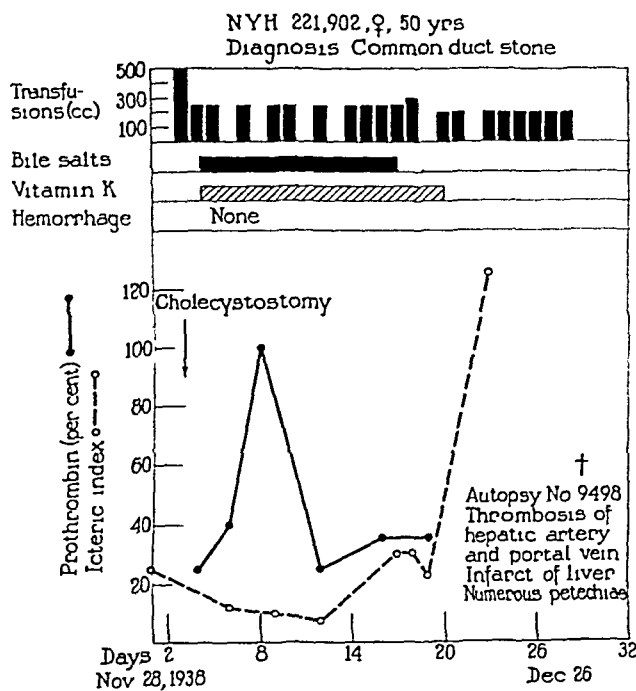


Fig. 2.—Failure of plasma prothrombin to respond to oral vitamin K therapy in a case of hepatic damage.

technic of its administration,²⁶ the factor of faulty gastrointestinal absorption, which may be present in some cases, can be eliminated (fig. 3). It is thus possible to utilize the response to menadione of patients with lowered plasma prothrombin levels as a measure of hepatic function.

During the past seven months, 28 patients with jaundice have been treated with menadione and the response of the plasma prothrombin determined. In 18 of the cases the jaundice was of the extrahepatic type (10 cases of common duct stone or cholangitis, 5 of carcinoma of the head of the pancreas and 3 of stricture of the common duct), while in 10 it was of intrahepatic origin. The diagnosis in 17 of the 18 cases in the first group was proved at operation, while in the eighteenth

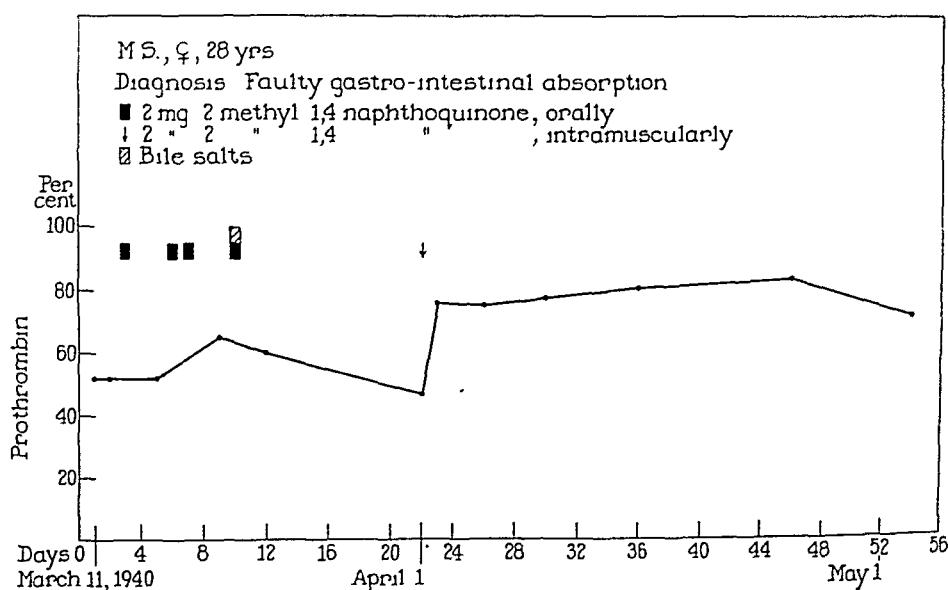


Fig. 3.—Response of plasma prothrombin to intramuscular administration of menadione.

case acute cholecystitis and gallstones were demonstrated later by the Graham test, and in this case the transient jaundice was apparently due to cholangitis. The patient in the last case refused to undergo operation.

Of the 10 patients with intrahepatic jaundice, 4 died and autopsies were performed, 3 were operated on and the disease in 2 of the remaining 3 ran a course typical of catarrhal jaundice, while the third is thought to have cirrhosis of the liver with hepatic insufficiency. This patient is still alive and has not been subjected to an operation.

26. Macfie, J. A.; Bacharach, A. L., and Chance, M. R. A.: The Vitamin K Activity of 2-Methyl-1, 4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, *Brit. M. J.* 2:1220 (Dec. 23) 1939. Andrus and Lord.²⁰

In table 3 are listed the 18 cases of extrahepatic jaundice. The diagnosis, duration of jaundice and icteric index are listed, as well as the preinjection level of plasma prothrombin and the twenty-four, forty-

TABLE 3.—*Jaundice of Extrahepatic Origin*

Case No.	Patient	Diagnosis	Duration of Jaundice	Icteric Index	Level of Plasma Prothrombin				Net Change, %
					Initial	After Injection, %			
						24 Hr.	48 Hr.	72 Hr.	
1	J. B.	Common duct stone	2 days	62	57	61	..	65	+ 8*
2	H. H.	Common duct stone	2 weeks	16	70	80	+10
3	J. M.	Carcinoma, head of pancreas	2 weeks	150	75	85	+10
4	M. P.	Common duct stricture	Off and on	75	61	72	..	73	+12†
5	P. D.	Carcinoma, head of pancreas	2 weeks	150	52	52	..	70	+18
6	F. G.	Common duct stone	3 months	60	66	85	+19
7	R. M.	Cholangitis; subacute cholecystitis and pancreatitis	2 days	33	76	95	..	95	+19
8	J. L.	Common duct stone	2 days	50	75	..	100	..	+25
9	K. H.	Carcinoma, head of pancreas	3 weeks	62	48	75	+27
10	L. M.	Acute cholecystitis; cholangitis	4 days	..	52	80	..	80	+28
11	C. G.	Cholelithiasis; cholangitis	2 weeks	26	52	75	80	..	+28
12	R. S.	Carcinoma, head of pancreas	1 month	125	52	71	71	90	+38†
13	S. F.	Carcinoma, head of pancreas	6 months	31	61	71	100	..	+39†
14	B. O.	Acute cholecystitis; cholangitis	1 week	28	60	100	+40
15	M. G.	Common duct stone	1 month	150	47	78	..	95	+48
16	K. F.	Common duct stone	1 week	25	52	..	100	..	+48
17	F. S.	Common duct stricture	3 weeks	150	18	67	50	..	+49
18	D. O.	Common duct stricture	3 months	150	38	70	..	100	+62

* This patient was operated on immediately after the initial prothrombin determination was made. The effect of operative trauma influenced the rise.

† These patients received more than one dose of menadione.

TABLE 4.—*Jaundice of Intrahepatic Origin*

Case No.	Patient	Diagnosis	Duration of Jaundice	Icteric Index	Level of Plasma Prothrombin				Net Change, %
					Initial	After Injection, %			
					24 Hr.	48 Hr.	72 Hr.		
1	A. G.	Cirrhosis with hepatitis	9 days	300	48	14	..	14	—34
2	J. D.	Cirrhosis with central necrosis	2 days	...	52	48	..	33	—19
3	P. L.	Cirrhosis	2 weeks	75	52	43	..	52	— 9
4	E. J.	Hepatic insufficiency	Unknown	60	41	..	36	..	— 5
5	E. T.	Catarrhal jaundice	3 days	107	71	..	70	..	— 1
6	G. G.	Abscess of the liver	4 days	75	52	52	0
7	M. S.	Catarrhal jaundice	2 weeks	60	67	..	68	..	+ 1
8	T. H.	Multiple abscesses of the liver	14	48	52	..	52	+ 4
9	S. M.	Catarrhal jaundice	3 weeks	100	70	76	+ 6
				225	76	0
					52	..	52	..	0
10	C. M.	Subacute hepatitis	10 days	40	60	60	70	65	+10

eight and seventy-two hour postinjection levels. The column on the right shows the percentage of change. As can be seen, in every case except 1 there was a rise of 10 per cent or more in the plasma prothrombin as a result of the intramuscular injection of menadione. Unfortunately, the patient in case 1, who showed a response of only

A brief résumé of case 5 follows:

A 39 year old white housewife had excellent health until five years before admission to the hospital, when she began to experience attacks of pain in the right upper quadrant of the abdomen, with nausea and vomiting, occurring every two to three months. In addition, she experienced marked postprandial flatulence and belching, made worse by fatty foods, cabbage, etc. There was no history of jaundice, chills or fever. Three weeks prior to admission the flatulence became much worse, and five days before admission the patient began to have severe pain in the right upper quadrant of the abdomen, radiating around the right costal margin and to the back. Dark urine and light stools were noted for ten days and jaundice for three days. The patient had vomited twice during the past ten days.

Physical examination showed moderate jaundice, with no discomfort. Examination revealed high in the right upper quadrant of the abdomen a firm, tender, rounded mass which descended on respiration. A tender lymph node was felt in the right groin. The urine contained occasional red and white blood cells and gave a 4 plus reaction for bile; the blood count was normal; the Kline reaction was negative; the icteric index was 107; the urea nitrogen of the blood was 7 mg. per hundred cubic centimeters; the stool was clay colored and negative for the presence of bile.

A flat roentgenogram of the abdomen showed what was interpreted as stones in the right upper quadrant of the abdomen and diagnosed by the department of roentgenology as cholelithiasis. The patient was given menadione and a high protein-high carbohydrate-low fat diet. An exploratory operation was performed April 29, 1940. The liver was found to be slightly enlarged; the common duct was not dilated, and there was no evidence of stones in the gallbladder or the common bile duct. Pressure on the gallbladder caused emptying without difficulty. The gallbladder was slightly thickened and was considered to be the seat of chronic cholecystitis. It was therefore removed.

The technic and interpretation of this new method of differentiating intra- and extrahepatic jaundice are as follows: A sample of blood for the determination of the initial level of plasma prothrombin is drawn, and immediately 2 mg. of menadione is injected intramuscularly. At the end of twenty-four hours a second sample of blood is examined, and if a rise of 10 per cent or more in the plasma prothrombin has occurred, the patient may be considered to have extrahepatic jaundice and no further determinations are necessary. On the other hand, if a rise of less than 10 per cent occurs, it is necessary to determine the plasma prothrombin level at either forty-eight or seventy-two hours after the injection. If the rise is then 15 per cent or more over the initial level, the patient probably has extrahepatic jaundice; if less than 15 per cent, the jaundice may be considered to be of intrahepatic origin and associated with definite damage to the liver.

Although this series numbers only 28 cases, the fact that this new method so far has been so uniformly accurate merits its serious consideration in the differential diagnostic armamentarium for dealing with patients with jaundice. The prothrombin test of Warner, Brinkhous and Smith,²² with its known accuracy, is best employed in this method,

the only other requirement being a supply of 2 mg. ampules of menadione in corn oil for intramuscular injection.

SUMMARY

A résumé of the more important laboratory aids for the differential diagnosis of intrahepatic and extrahepatic jaundice is presented.

The evidence that the plasma prothrombin is intimately related to the functional state of the liver is reviewed.

The response of the plasma prothrombin to intramuscular injection of menadione is recommended as an excellent differential diagnostic aid in cases of jaundice, since in a series of 28 cases, 10 of which were instances of intrahepatic and 18 of extrahepatic jaundice, the test was almost uniformly accurate.

NOTE.—Since this paper was submitted for publication 12 more cases of extrahepatic jaundice have been observed, and in every case except 1 the response was as anticipated. In the remaining case the plasma prothrombin rose only 9 per cent. However, this response may have been influenced by the fact that the patient was operated on immediately after the initial determination had been made.

We have observed 6 additional cases of intrahepatic jaundice, in 4 of which the test was accurate. In 1 of the 2 remaining cases the patient had catarrhal jaundice, which was confirmed at operation. The test was employed on two occasions during the period of preoperative study and on the first application the plasma prothrombin rose 29 per cent, while two weeks later it fell 9 per cent.

In the second case two initial determinations revealed levels of 43 and 53 per cent of normal. After the injection of menadione the prothrombin rose to 100 per cent. It was this case which led to the following slight revision in the technic of the test:

The initial level of plasma prothrombin is determined on two successive days, and if the two levels are within 5 per cent of each other, 2 mg. of menadione is injected intramuscularly and the prothrombin is determined at intervals of twenty-four, forty-eight and seventy-two hours, as already indicated. On the other hand, if there is a difference greater than 5 per cent in the two initial levels of prothrombin, the level is determined on the third day and so on until the levels on two successive days are found to be within 5 per cent of each other. When such agreement occurs, the menadione is administered. We have on no occasion found it necessary to determine the prothrombin for more than three successive days before injection of menadione.

Finally, in the interpretation of the test we have observed that every case of jaundice in which the initial level of plasma prothrombin was 80 per cent or more has been one of extrahepatic jaundice.

TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH SULFANILAMIDE AND SULFAPYRIDINE

A STATISTICAL STUDY OF ALL REPORTED CASES IN WHICH
CHEMOTHERAPY WAS USED, WITH OR WITHOUT
SPECIFIC ANTIPNEUMOCOCCUS SERUM

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The mortality rate from pneumococcic meningitis was practically 100 per cent previous to 1937. Goldstein and Goldstein¹ in a review of the literature up to 1927 collected only 150 authentic reports of recovery from this disease. Of a series of 468 patients with bacterial meningitis admitted to the State Charity Hospital of Louisiana in the ten year period prior to 1936, Tripoli² reported that illness in 111 was due to pneumococci and that 110 died, a mortality rate of 99 per cent. Toomey and Roach³ reported that 157 patients with pneumococcic meningitis were admitted to the Cleveland City Hospital between 1922 and 1939 and that they all died irrespective of treatment.

When effective concentrated type-specific antipneumococcus horse serum became available about 1930, the antibodies were used in an attempt to treat pneumococcic meningitis. That the results were disappointing was shown by the fact that the *Quarterly Cumulative Index Medicus* listed reports of only 30 additional recoveries during the period from 1927 to 1939. The majority of these few cures were attributed to spinal drainage, to the administration of antipneumococcus serum or the administration of ethylhydrocupreine hydrochloride, or to a combination of these therapeutic measures.

Perhaps one of the most important reasons for the discouraging results with antipneumococcus horse serum was to be found in the fact that the molecule of the horse serum was large and evidently did not

1. Goldstein, H. I., and Goldstein, H. Z.: Pneumococcus Meningitis and Endocarditis: Report of Twenty Cases of Pneumococcic Meningitis With and Without Pneumococcic Endocarditis; Consideration of Treatment and Review of the Literature, *Internat. Clin.* **3**:155 (Sept.) 1927.

2. Tripoli, C. J.: Bacterial Meningitis: A Comparative Study of Various Therapeutic Measures, *J. A. M. A.* **106**:171 (Jan. 18) 1936.

3. Toomey, J. A., and Roach, F.: Pneumococcus Meningitis, *Ohio State M. J.* **35**:841 (Aug.) 1939.

pass into the cerebrospinal fluid from the blood stream. As a consequence, it was necessary to inject the horse serum antibody intrathecally, where it produced a violent foreign protein reaction in the form of fibrin and leukocytes with resultant block of fluid drainage and antibody diffusion and formation of localized abscess pockets.

It was expected that the smaller molecule of antipneumococcus rabbit serum might enter the cerebrospinal fluid directly from the blood stream and thus eliminate the necessity for intrathecal administration. Confirmatory evidence that there may be such a diffusion of antibodies seems to be limited to an observation made by one of us (J. G.) of swelling of capsules in pneumococci removed in the spinal fluid twenty-four hours after intravenous administration of 80,000 units of type XVIII antipneumococcus rabbit serum.⁴ Negative evidence has been presented by Finland, Brown and Rauh⁵ who were unable to demonstrate pneumococcus antibodies (agglutins or mouse protection) in the cerebrospinal fluid after intravenous injection of antipneumococcus horse or rabbit serum, in either the presence or the absence of pneumococcic meningitis.

Renewed interest in chemotherapy was awakened by the introduction of sulfanilamide. Pneumococcic pneumonia was one of the numerous bacterial diseases treated with this drug, but statistically the medicament proved definitely effective only against the type III pneumococcus. A perusal of table 1 will at once reveal the startling fact that this same drug has proved much more effective in treatment of pneumococcic meningitis than it was against pneumonia. Table 1 includes a summary of the 48 reported cases of pneumococcic meningitis treated with sulfanilamide and azo derivatives from January 1937 to June 1940.

4. W. H., aged 7, entered the hospital on Dec. 17, 1938. The complaint was a stiffness in the neck of twenty-four hours' duration. The patient was semicomatose, had a stiff, retracted neck and exhibited a positive Kernig sign. Lumbar puncture done at 4:30 p. m. on the day of entry to the hospital yielded cloudy fluid under increased pressure. Examination of the fluid gave a negative reaction for sugar, a positive reaction for globulin and a cell count of 230; type XVIII pneumococci were present in the spinal fluid on direct smear. Treatment consisted of the intravenous administration of 80,000 units of type XVIII rabbit serum. About twenty-four hours later, at 4 p. m. on December 18, fluid obtained in a second lumbar puncture gave a negative reaction for sugar, a reaction indicating a large trace of globulin, and a cell count of 3,100. On direct smear of this fluid it was observed that the capsules of the pneumococci were swelled. This patient died on December 19, the third day after entry to the hospital and the fourth day after the onset of the illness.

5. Finland, M.; Brown, J. W., and Rauh, A. E.: Treatment of Pneumococcus Meningitis: A Study of Ten Cases Treated with Sulfanilamide Alone or in Various Combinations with Specific Anti-Pneumococcic Serum and Complement, Including Six Recoveries, *New England J. Med.* **218**:1033 (June 23) 1938.

It would appear from the lack of any reports in the recent literature that sulfanilamide and azo derivatives have been largely abandoned in favor of sulfapyridine in the treatment of pneumococcic meningitis (table 2). It has been erroneously assumed that sulfapyridine is the more effective drug against all pneumococcic infections because of its demonstrated superiority in pneumococcic pneumonia.

In table 3 the results of the two forms of chemotherapy have been listed according to the type of the causative pneumococcus. It should be noted that deaths have been separated into two groups, namely, those occurring before the end of the first twenty-four hours and those occurring after twenty-four or more hours of chemotherapy. At the end of the chart the total number of recoveries and the total number of deaths have been listed. The percentage of recoveries has been calculated with and without the inclusion of those patients who died within the first twenty-four hours.

Table 4 presents data on the use of the two drugs, including both recoveries and deaths and with special attention directed to the presence or absence of septicemia and to division of patients into age groups above and below 13 years. A separate listing is made in the sulfapyridine series for patients under 1 year of age, but no such grouping was made in the sulfanilamide series, as only 1 case of a patient under 2 years of age was reported.

REPORT OF A CASE

The following report of a case of pneumococcic meningitis emphasizes the numerous problems in question.

A 26 year old white man entered the hospital complaining of malaise, fever, headache, a stiff neck, thick speech, nausea and vomiting. Physical examination revealed a temperature of 103 F., a pulse rate of 100, a respiratory rate of 38, a stiff neck, generalized muscular rigidity, thick speech, unsteady gait and profuse sweating. Lumbar puncture yielded cloudy fluid under increased pressure. Gram-positive and lancet-shaped diplococci were found on direct smear and showed swelling of the capsules when mixed with type XIX diagnostic pneumococcus serum. A total of 285,000 units of type XIX antipneumococcus rabbit serum was given intravenously in divided doses over a forty-eight hour period. Eight cubic centimeters of complement (patient's own serum) was administered intrathecally at the end of a second lumbar tap. Administration of sulfapyridine was begun about eight hours after the patient entered the hospital, and a total of 15 Gm. in divided doses was given through a stomach tube at four hour intervals. The level of sulfapyridine in the blood did not exceed 5 mg. per hundred cubic centimeters, and the level in the spinal fluid did not exceed 2.75 mg. Blood cultures were positive for the type XIX pneumococcus.

There was a temporary moderate fall in temperature and some clinical improvement at the end of the first twenty-four hours in the hospital. A sudden reversal followed, and the temperature and the pulse rate rose. Pulmonary congestion and peripheral circulatory failure developed. The patient died forty-eight hours after his admission to the hospital.

TABLE 1.—Summary of Pertinent Data in Forty-Eight Reported Cases of Pneumococcic Meningitis in Which Treatment Was with Sulfanilamide and Azo Derivatives

Reference	Age, Years	Type of Pneumococcus	Drug	Total Dose	No. Days Administered	Level of Drug in Blood, Mg./100 Cc.	Level of Drug in Spinal Fluid, Mg./100 Cc.	Blood Culture	Spinal Fluid Culture	Administration of Serum	Result	Postmortem Findings
Caldwell, J. R., and Byrne, P. S.: Brit. M. J. 1: 1204 (June 12) 1937	16	I	Azosulfamide,* p.o. and i.m.	..	4+	Smears positive	..	Recovery	
Mertins, P. S., and Mertins, P. S., Jr.: Arch. Otolaryng. 25: 657 (June) 1937	13	IV	Azosulfamide*..... Sulfanilamide, p.o....	240 cc. 6 Gm.	6 3	Recovery	
Tixier, L.; Eck, M., and Grosard: Bull. Soc. de pédiat. de Paris 36: 118 (March) 1938.	9	V	Sulfanilamide, i.m., i.h., s.c. and i.s.	82 Gm.	18	4-11	..	Sterile	Sterile after 9 days	One dose of antipneumococcus serum, i.s.	Recovery	
Mitchell, A. G., and Trachsler, W. H.: J. Pediat. 11: 183 (Aug.) 1937	Not given (child)	V	Sulfanilamide.....	12.6 Gm.	7	Positive at onset	Ethylhydrocupreine	Recovery	
Dasman, J., and Perley, A. M.: J. Pediat. 11: 213 (Aug.) 1937	9	V	Sulfanilamide, p.o.... i.t..... Azosulfamide, i.m....	72 Gm. 13.4 Gm. 60 cc.	18	4.2-11.5	9.6	Sterile	Sterile after 9 days	Antimen-ingococcus serum, 50,000 units i.v. and 15 cc. i.m.	Recovery	
8	III		Azosulfamide,* i.m.. Sulfanilamide, p.o....	360 cc. 26 Gm.	13	Positive throughout	Antimen-ingococcus serum, 50,000 units	Death	Not given
12	Not typed		Azosulfamide*.....	10 cc.	One dose	Death before adequate treatment could be started	
Millett, J.: J. A. M. A. 109: 2193 (Dec. 25) 1937	53	III	Azosulfamide,* i.t.... i.m.....	60 cc. 60 cc.	1 1	Positive	..	Death	Large pituitary tumor that oozed pus
Neal, J. B., and Applebaum, E.: Am. J. M. Sc. 195: 175 (Feb.) 1938	..	XXI	Original prontosil,† p.o.; sulfanilamide, p.o.	Recovered	
..	XXIV		Original prontosil †; sulfanilamide	Recovered	
..	IV		Original prontosil †; sulfanilamide	Recovered	

* Disodium 4-sulfamidophenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3'-G-disulfonate.
† A hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene.

11	Tuxier, L.; Eck, M., and Gros-sard: Bull. Soc. de pédiat. de Paris 36: 113 (March) 1938	I	Sulfanilamide, p.o....	19 Gm.	12	Sterile on third day	..	Recovered
26	Latto, C.: Brit. M. J. 1: 563 (March 12) 1938	I	Azosulfamide *.....	Large doses	Positive for 12 days	..	Recovered
5	Landon, J.: Brit. M. J. 1: 841 (April 16) 1938	Not typed	Azosulfamide,* i.m..	80 cc.	1	First culture positive; second one, 21 days later, negative	..	Recovery
17	Hubert, C.: Rev. de laryng. 59: 365 (April) 1938	III	Sulfanilamide, p.o....	101 Gm.	Sterile after third day	..	Recovery
43	Boyd, L. J.; Baron, B., and Selachman, M.: New York M. Coll. & Flower Hosp. Bull. 1: 99 (June) 1938	II	Azosulfamide,* i.v.... i.m.....	10 cc. 40 cc.	4	Sterile	90,000 units of meningococcus anti-toxin i.v. and 117 cc. of anti-meningococcus serum i.s.; antipneumococcus serum i.s. and i.v. for 5 days	Recovery
14		II	Azosulfamide *..... Sulfanilamide (0.8% sol.) i.s.	10 cc. 20 cc.	Sterile	Antimen-gococcus serum i.m. and i.v.; antipneumococcus serum i.s.	Recovery
19	Finland, Brown and Rauh s....	XVII	Sulfanilamide, p.o....	325 Gm.	63	5 - 15	..	Sterile	Sterile in 5th week	Recovery
8		VII	Sulfanilamide, p.o....	70 Gm.	20	10 - 12	..	Sterile	Sterile on 5th day	Recovery
7		XIX	Sulfanilamide, p.o....	51 Gm.	8	10 - 20	..	Sterile	Sterile in 48 hours	Recovery
13		XXVIII	Sulfanilamide, p.o....	106 Gm.	14	15	..	Sterile	Sterile on 3rd day	Recovery

TABLE 1.—Summary of Pertinent Data in Forty-Eight Reported Cases of Pneumococcic Meningitis in Which Treatment Was with Sulfanilamide and Azo Derivatives—Continued

Reference	Age, Years	Type of Pneumococcus	Drug	Total Dose	No. Days Administered	Level of Drug in Blood, Mg./100 Cc.	Level of Drug in Spinal Fluid, Mg./100 Cc.	Blood Culture	Spinal Fluid Culture	Administration of Serum	Result	Postmortem Findings
Allan, W. B.; Mayer, S., Jr., and Williams, R.: <i>Am. J. M. Sc.</i> 196: 99 (July) 1938	17	XXVIII	Sulfanilamide, p.o....	189 Gm.	25	10 - 12	..	Sterile	Sterile on 13th day	Autogenous serum i.s.	Recovery	
	10	III	Sulfanilamide, p.o....	84 Gm.	15	8 - 10	..	Sterile	Sterile on 11th day	Autogenous serum i.s.	Recovery	
	19	XI	Sulfanilamide, p.o.... s.c..... i.s.....	105 Gm. 3 Gm. 2.5 Gm.	19	Positive	Positive	Fresh human serum i.s.	Death	Purulent meningitis; frontal cortical abscess; bronchopneumonia
	47	XXI	Sulfanilamide, p.o....	92 Gm.	23	Positive	Positive	..	Death	None
3	43	VII	Sulfanilamide, p.o....	42 Gm.	6	4 - 5	..	Positive	Positive	Specific serum i.v.; normal serum i.s.	Death	Purulent meningitis; lobar pneumonia
		IV	Sulfanilamide, p.o....	12 Gm.	36	Positive	Positive	Antipneumococcus rabbit serum i.v.; normal serum i.s.	Death in 36 days	Purulent meningitis; congestion of lungs
		XIV	Sulfanilamide, p.o....	35.6 Gm.	8	5 - 7	..	Sterile	Sterile after 24 hours	..	Recovery	
42		XXIV	Sulfanilamide, p.o....	43.7 Gm.	10	4.5 - 10	5.8	Sterile	Sterile on 2nd day	..	Recovery	
	18	XX	Sulfanilamide, p.o., s.c. and i.s.p.	35 Gm.	5	6 - 10.7	3 - 8	Sterile	Sterile on 4th day	Antimeningococcus serum i.s.	Recovery	
5		Not typed	Sulfanilamide, p.o....	10.5 Gm. 6.0 Gm. 6.5 Gm.	5 3 3	Sterile on 7th day	Antimeningococcus serum i.s. (10 cc.)	Recovery	
		III	Sulfanilamide, p.o....	96 Gm.	37	6 - 14	4.2 - 8.2	..	Sterile on 14th day	..	Recovery	
Gubner, J.: <i>Arch. Otolaryng.</i> 28: 241 (Aug.) 1938	5½											
Querry, R. Z.: <i>J. A. M. A.</i> 111: 1373 (Oct. 8) 1938	33	VII	Sulfanilamide, p.o....	200.2 Gm.	16	10 - 25	8 - 10 mgs.	Positive	Sterile after 5 days	Type-specific serum, 820,000 units i.v. and i.s.	Recovery	

Hewell, B. A., and Mitchell, A. G.: J. A. M. A. 112: 1033 (March 18) 1939	9	V	Sulfanilamide, p.o....	27 Gm.	7	Sterile	Sterile on 3rd day	Ethylhydro- cupreine, 2.7 Gm.	Recovery
	10	III	Sulfanilamide, p.o., i.v. and i.s.	21 Gm.	7	10	..	Sterile	Sterile on 4th day	Ethylhydro- cupreine, 0.7 Gm.	Recovery
	8	III	Sulfanilamide, p.o....	61 Gm.	17	8-12	..	Sterile	Sterile on 3rd day	Ethylhydro- cupreine, 1.6 Gm.	Recovery
	7	III	Sulfanilamide, p.o. and 0.8% sol., i.v. and i.s.	33 Gm.	10	Positive	Positive	..	Death
	2 mo.	VII	Sulfanilamide, p.o....	6 Gm.	Positive	Positive	Ethylhydro- cupreine, in large doses; specific serum i.m.	Death
	9	III	Sulfanilamide, p.o.; 0.8% sol., i.v. "Prontosil" (form not stated)	61 Gm. 60 cc.	13	7-9	Antipneu- mococcal serum	Death
Gray, R. C., and Adams, B.: Minnesota Med. 22: 369 (June 1939)	19	IV	Sulfanilamide, p.o. and i.v.	69 Gm.	18	3.0-5.3	Sterile after 11th day	Antipneu- mococcal rabbit serum, 420,000 units	Recovery
Toomey and Roach ³	71	III	Sulfanilamide.....	34 Gm.	8	Sterile	Sterile after 2nd day	Antipneu- mococcal serum, 100,000 units	Recovery from meningitis
Silverman, D., and Thorner, M.: Arch. Otolaryng. 30: 431 (Sept.) 1939	47	III	Sulfanilamide.....	32.3 Gm.	8 in hospital	Sterile on 8th day	None	Recovery for 4 mo.
	20	III	Sulfanilamide; azosulfamide*	Not given	8 in hospital	Positive	Not given	None	Death
	56	III	Sulfanilamide.....	Not given	2 in hospital	Death
	49	III	Sulfanilamide.....	Not given	92 in hospital	Positive	Death
	33	III	Sulfanilamide.....	Not given	13 in hospital	Sterile	Death
	47	III	Sulfanilamide.....	Not given	147	Sterile	Death
Welch, S. H., and Martin, H.: F.: J. Pediat. 115: 563 (Oct.) 1939	9	III	Sulfanilamide, p.o.... i.m..... Original prontosil +	270 Gm. 145 cc.	35 6	2-9	5 7	..	Sterile after 14 days but temporarily positive after relapse	..	Recovery

TABLE 2.—Summary of Pertinent Data in Sixty-Seven Reported Cases of Pneumococcic Meningitis in Which Treatment was Chiefly with Sulfapyridine

Reference	Age, Years	Type of Pneumococcus	Drug	Total Dose	No. Days Administered	Level of Drug in Blood, Mg./100 Cc.	Level of Drug in Spinal Fluid, Mg./100 Cc.	Blood Culture	Spinal Fluid Culture	Administration of Serum	Result	Postmortem Findings
Feld, G. O. K., and Dyke, S. O.: Lancet 2: 619 (Sept. 10) 1938	7	Not typed	Sulfapyridine, p.o....	22.5 Gm.	6	Sterile after 24 hours	..	Recovery	
Cunningham, A. A.: Lancet 2: 1174 (Nov. 12) 1938	47	I	Sulfapyridine, p.o.... Sulfanilamide.....	50 Gm. 15 Gm.	7½ 1½	6.5-15.5	3.8-8.5	..	Sterile after 4 days	..	Recovery	
Robertson, K.: Lancet 2: 728 (Sept. 24) 1938	14	Not typed	Solusseptasine,* i.v.... Sulfapyridine.....	20 cc. 40 Gm.	8+	Sterile after 48 hours	Polyvalent (I and II) Felton's serum, 40,000 units	Recovery	
McAlpine, D., and Thomas, G. C.: Lancet 1: 754 (April) 1939	24	Not typed	Sulfapyridine, p.o....	25.5 Gm.	7	..	Trace - 3 mg.	..	Sterile on 3rd day	..	Recovery	
Barnett, H. L.; Hartmann, A. P.; Ferley, A. M., and Ruhoff, M. B.: J. A. M. A. 112: 518 (Feb. 11) 1939	?	V	Sulfapyridine.....	Recovery	
Yule, A. P.: Brit. M. J. 1: 872 (April 20) 1939	15	Not typed	Sulfapyridine..... Sulfapyridine, p.o. and i.m. Proseptasine,† p.o....	.. 52 Gm.	.. 14 Sterile after 3 days	Death after 16 days Recovery	
Cutts, Gregory and West ¹³	14	XX	Sulfapyridine.....	100 Gm., approximately	26	2.2	1.7	Sterile	Sterile after 15 days	Complement and specific serum	Recovery	
May, K.: Lancet 1: 1100 (May 13) 1939	2½	X	Sulfapyridine.....	12.5 Gm., approximately	8	..	3.4	..	Positive	..	Death	
Raman, P. S.: Lancet 1: 1101 (May 13) 1939	34	Not typed	Sulfapyridine, 1st course 2nd course	80 Gm. 75 Gm.	15 11	Sterile after 15 days	Positive for 19 days	..	Recovery	
MacKeith, R. O., and Oppenheimer, G.: Lancet 1: 1069 (May 13) 1939	28	IV	Sulfanilamide..... Sulfapyridine.....	6 Gm. 12 Gm.	1 5	..	1.55	Sterile after 4 days	Sterile after 6 days	..	Recovery	
	59	Not typed	Sulfapyridine.....	4 Gm.	24	Positive	Positive	..	Death	Sulci filled with green pus; congestion but no exudate at base of brain
	30	III	Sulfapyridine.....	40 Gm. 30 Gm.	10 10	Sterile	Sterile after 7 days	..	Recovery	
	53	Not typed	Sulfapyridine.....	11 Gm.	2	Positive	..	Death	Sulci filled with pus

* Disodium p-(γ-phenylpropylamino)-benzenesulfonamido-α-γ-disulfonate.
† Parabenzyllumbenzenesulfonamide (benzyl sulfanilamide).

	6	Not typed	Sulfapyridine.....	1 Gm.	3	Positive	..	Death 5 days after admission to hospital	Slight haziness of meninges at base of brain; convulsions swollen and sulci obliterated
Cable ^{1a}	7	X	i.m..... Sulfapyridine, p.o...	7.3 Gm. 0.25 Gm. 2 Gm.	7 2 2	Sterile after 7 days	..	Recovery	
Toomey and Roach ³	38	IV	Sulfapyridine.....	14 Gm.	Death 16 hours after drug administered	
	2½ mo.	XVIII	Sulfanilamide..... Sulfapyridine.....	11.8 Gm. 5 Gm.	4	Specific serum, 100,000 units	Death	Meningitis; septi- cemia; purulent labyrinthitis
	18 mo.	Not typed	Sulfanilamide..... Sulfapyridine.....	3.3 Gm. 18 Gm.	4	Death	Suppurative leptomeningitis; thrombosed sinus
	28	VII	Sulfapyridine.....	10 Gm.	1	Positive	Antipneumococcus horse serum (VII and V), 120,000 units	Death	
	32	XVIII	Sulfanilamide..... Sulfapyridine.....	25.3 Gm. 23 Gm.	17	Rabbit serum, 100,000 units	Death	Purulent meningitis
	62	XIV	Sulfapyridine.....	33.5 Gm.	9	Sterile after 4 days	..	Recovery from meningitis	
	31	XIII	Sulfapyridine.....	57 Gm.	8	Sterile after 6 days	Sterile after 7 days	Rabbit serum, 200,000 units	Recovery	
	12	V	Sulfapyridine..... Sulfanilamide.....	34 Gm. 6.3 Gm.	15	Sterile on 5th day	Rabbit serum, 100,000 units	Recovery	
	15	V	Sulfanilamide..... Sulfapyridine.....	30 Gm. 27 Gm.	4 5	Sterile on 4th day	Rabbit serum, 100,000 units	Recovery	
	48	III	Sulfapyridine.....	57 Gm.	12	Positive	Intermittently positive	..	Death	Suppurative meningococcal meningitis; acute vegetative endocarditis; acute bronchitis; bronchopneumonia
	29	V	Sulfanilamide..... Sulfapyridine.....	14.6 Gm. 30 Gm.	2 14	Recovery	
Hodes, Gumble and Burnett ^{10a}	34	XXV	Sulfapyridine.....	1.7 - 4.8	1.1 - 4	Positive	Sterile after 18 days	..	Recovery	

TABLE 2.—Summary of Pertinent Data in Sixty-Seven Reported Cases of *Pneumococcic Meningitis* in Which Treatment was Chiefly with Sulfapyridine—Continued

Reference	Age, Years	Type of Pneumococcus	Drug	Total Dose	No. Days Drug Administered	Level of Drug in Blood, Mg./100 Cc.	Level of Drug in Spinal Fluid, Mg./100 Cc.	Blood Culture	Spinal Fluid Culture	Administration of Serum	Result	Postmortem Findings
	7	I	Sulfapyridine.....	Sterile	Sterile after 2 days	..	Recovery	
	11	V	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	Sterile	Sterile after 1 day	..	Recovery	
	32	IX	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	3.2 - 8.0	2.7 - 4.0	Sterile	Sterile after 2 days	..	Recovery	
	49	XXIII	Sulfapyridine, p.o., i.v.	1.8 - 2.5	1.3 - 13.3	Positive	Sterile after 10 days	..	Recovery	
	35	XII	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	4.1 - 14	4.5 - 7.5	Positive	Sterile after 5 days	..	Recovery	
	45	III	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	11.0 - 28.5	13.0 - 20	Sterile	Sterile after 11 days	..	Recovery	
	11	III	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	11.1 - 15.3	5.8 - 15	Positive	Sterile after 3 days	..	Recovery	
	6	XXVII	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	Trace - 8.7	Trace - 5.2	Sterile	Positive for 3 days	..	Death	Cerebellar abscess
	28	XII	Sulfapyridine, p.o....	Positive	Positive	..	Death in less than 24 hours	
	9 mo.	VI	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	Positive	Positive	..	Death in less than 24 hours	
	5 mo.	XXIX	Sulfapyridine, p.o....	10.4	7.5	Positive	Positive	..	Death in less than 24 hours	
	1	VI	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	10.0 - 30.3	..	Positive	Positive	..	Death in less than 24 hours	
	10 mo.	XIV	Sulfapyridine, p.o....	8.2	6.4 - 11.4	Positive	Positive	..	Death	
	31	XXII	Sulfapyridine, p.o....	4.7 - 10.5	1.9 - 7.5	Sterile	Positive	..	Death	
	12	XIX	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	12 - 29	Sterile	Positive	..	Death	
	54	XXXI	Sulfapyridine, p.o.; sodium sulfapyridine, i.v.	Sterile	Positive	..	Death	

Klemperer, W. W.: Canad. M. A. J. 41: 585 (Dec.) 1939	11	III	Sulfapyridine, p.o...	72.2 Gm.	18	10 - 15	Sterile after 7th day	Rabbit serum, 100,000 units	Recovery
Robertson, F. J.: Brit. M. J. 2: 995 (Nov. 18) 1939	23	XIX	Sodium sulfapyridine, i.m. and p.o.	1 Gm. 36 Gm.	Sterile after 3rd day	..	Recovery
Holmes, J. G.: Brit. M. J. 2: 995 (Nov. 18) 1939	38	IV	Sulfapyridine, p.o...	27 Gm.	5	Sterile after 4 days	..	Recovery
Christien, H. S.; Jorgenson, G. M., and Ellis, C.: Am. J. Dis. Child. 59: 1 (Jan.) 1940	3 mo.	XXIV	Sulfapyridine.....	350 mg. per kilo-gram per day	5	7 - 10.2	6.3	Positive	..	Rabbit serum, 250,000 units	Death
	11 mo.	XIV	Sulfapyridine.....	270 mg. per kilo-gram per day	22 hr.	13.5 - 19.3	8.0 - 11.3	Positive	Death in less than 24 hours
Moore, M. L., and Forbes, R. P.: J. Pediat. 16: 347 (March) 1940	5	XVIII	Sulfapyridine, p.o. and i.v.	113 Gm.	15	Trace - 16.3	Sterile after 7 days	..	Recovery
Reid, W. O., and Lipscomb, J. F.: Brit. M. J. 1: 802 (May 18) 1940	19	XIX	Sulfapyridine..... sodium sulfapyridine, i.m.	68.5 Gm.	16	6 - 15	4 - 10	Recovery
Elvidge, A. R., and Roseman, E.: Canad. M. A. J. 42: 460 (May) 1940	33	XXIII	Sulfapyridine, p.o. and i.v.	239 Gm.	67 (Intermittently)	Last positive culture 34 days after onset	Rabbit serum, 400,000 units	Recovery
	7	I	Sodium sulfapyridine	48 Gm. 20 Gm.	5 6	Sterile after 5th day	..	Recovery
Falla ^{18c}	10	Not typed	Sodium sulfapyridine	19 Gm.	20	Death
	39	Not typed	Sodium sulfapyridine	48 Gm.	Death
	?	Not typed	4 additional cases; details not given beyond mention of death								
McKay and Hurteau ¹⁴	8	I	Sulfapyridine.....	53 Gm.	14	4.2 5.8	1.7 - 3.6	..	Positive	Rabbit serum, 100,000 units	Recovery
	39	III	Sodium sulfapyridine i.v. and i.m.; sulfapyridine, p.o.	105 Gm.	10	1.7 - 5.4	1.2 - 4.1	..	Sterile after 20 hours	Rabbit serum, 300,000 units	Recovery
	52	Not typed	Sodium sulfapyridine; sulfapyridine, i.v., i.m. and p.o.	375 Gm.	50	Trace - 10.8	Trace - 0.9	..	Sterile after 28 days	..	Recovery
	53	XXIII	Sulfapyridine.....	83 Gm.	28+	Rabbit serum, (twice)	Recovery
Kolmer ^{17a}	?	?	Reports 3 cases (1 recovery)		
Steele, O. W.; Gottlieb, J., and Brann, H.: J. Maine M. A. 31: 315 (Dec.) 1940	26	XIX	Sulfapyridine.....	15 Gm.	2	5	2.75	Positive	Positive	Type-specific rabbit serum, 285,000 units	Death
											Meningitis; cerebral thrombosis

TABLE 3.—Summary of Recorded Results of Treating Pneumococcic Meningitis with Sulfanilamide and Azo Derivatives and with Sulfapyridine

Type of Pneumococcus	Sulfanilamide and Azo Derivatives						Sulfapyridine					
	Recoveries		Deaths Under Twenty-Four Hours		Deaths Over Twenty-Four Hours		Recoveries		Deaths Under Twenty-Four Hours		Deaths Over Twenty-Four Hours	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
I.....	3	100	4	100
II.....	2	100
III.....	8	47	1	6	8	47	5	83.33	1	16.66
IV.....	3	75	1	25	2	66.66	1	33.33
V.....	4	100	5	100
VI.....	2	100
VII.....	2	66%	1	33%
VIII.....	1	100
IX.....
X.....	1	100
XI.....	1	50	1	50
XII.....	1	100
XIII.....	1	50	1	50
XIV.....	1	100	1	100
XV.....	1	100	1	25	2	50	1	25
XVI.....
XVII.....
XVIII.....	1	33%	2	66%
XIX.....	1	100	2	50	2	50
XX.....	1	100	1	100
XXI.....	1	100
XXII.....
XXIII.....
XXIV.....	2	50	3	100	1	100
XXV.....	1	50
XXVI.....	1	100
XXVII.....	1	100
XXVIII.....	2	100
XXIX.....	1	100
XXX.....
XXXI.....	1	100
Not typed.....	2	66.66	1	33.33	1	100
Total.....	33		2		13		7	36.85	2	11.53	10	51.32
							36		9		22	

Analysis of table 3 will show that 33, or 68.75 per cent, of the patients recovered and 15, or 31.25 per cent, of the entire group treated with sulfanilamide and azo derivatives whereas 36, or 53.7 per cent, recovered and 31, or 46.2 per cent, died of the entire group treated with sulfapyridine. When the patients who died in less than twenty-four hours are excluded from each group, the percentage of recoveries among patients treated with sulfanilamide and azo derivatives becomes 71 as contrasted to a percentage of 62.7 among those treated with sulfapyridine.

Autopsy performed six hours after death showed marked lividity and rigor mortis and a purplish discoloration about both auriculae, the oral cavity, the neck and the finger nail beds. The face presented a sunken appearance. There was marked congestion of all organs and an excess of watery sanguineous fluid escaping on section. The right auricle and the superior and inferior venae cavae were distended. An edematous brain which weighed 1,680 Gm. presented a fibrinous exudate with approximately 25 cc. of turbid fluid at its base. The spleen was enlarged; the capsule was tense and there was excessive sanguineous pulp. A moderately enlarged, smooth, firm, tense liver was found. The kidneys appeared slightly granular after the capsule was stripped off. Both pleural cavities were

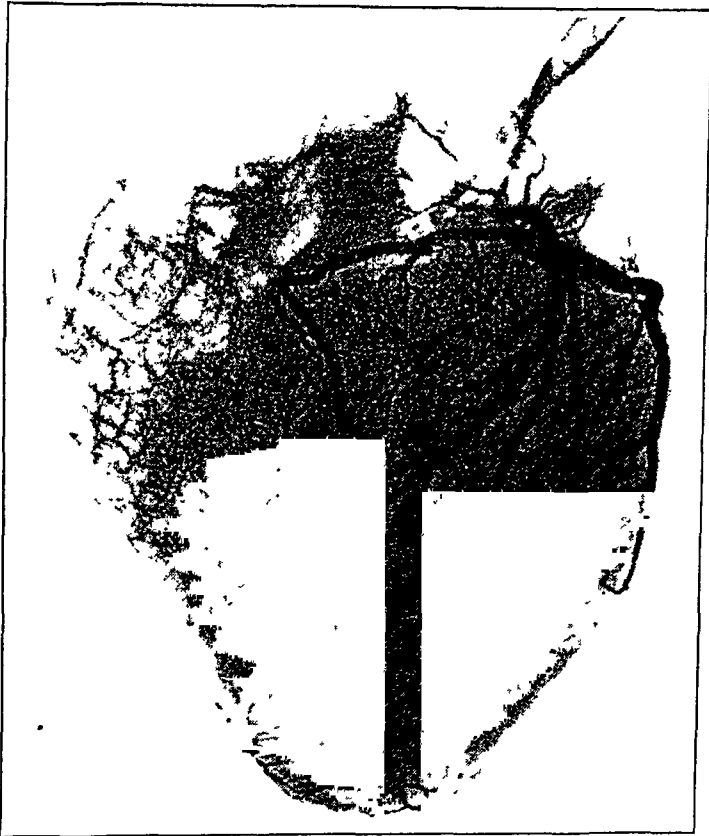


Fig. 1.—Normal heart and coronary circulation, shown by visualization technic, in the presence of circulatory collapse. The right auricle, however, is probably distended.

free from adhesions and were occupied by 20 to 30 cc. of clear yellow serous fluid. Both lungs were doughy and edematous and on pressure pitted and had an excess of sanguineous frothy fluid escaping. The dependent portions were moist, soggy and heavy. A small indurated area involving the left lung at its anterior aspect was found at its lateral periphery. Both pleurae showed numerous petechial ecchymotic and hemorrhagic areas. Similar lesions were present on the posterior surface of the ventricles. Inspection and visualization studies of the coronary arteries revealed nothing abnormal. Serial section and visualization studies of the right lung failed to reveal induration or consolidation. The right middle ear was occupied by a slightly turbid watery fluid. Cultures of the heart, the middle ear, the lungs, the spleen and the fluid at the base of the brain were positive for pneumo-

cocci; the capsules of the organism swelled with type XIX antipneumococcus serum.

Microscopic examination revealed foci of cerebral thrombosis (fig. 3) and patches of early bronchopneumonia and confirmed macroscopic findings.



Fig. 2.—Right lung, demonstrated by visualization technic, showing a relatively normal lung in the presence of a continued pneumococcic bacteremia.



Fig. 3.—Thrombosis of cerebral vessel and meningitis; high magnification, $\times 200$.

Summary.—The following diagnosis was made: type XIX pneumococcic meningitis with septicemia; toxic nephrosis; toxic splenitis; toxic myocarditis with right-sided cardiac failure; acute circulatory collapse; cerebral thrombosis; early

bronchopneumonia, and marked pulmonary edema. The causes of death were pneumococcic meningitis with circulatory collapse and cerebral thrombosis, and septicemia. The original focus of infection was probably the right middle ear.

Comment.—It is of interest to note that the *Quellung* phenomenon in vitro was still present after the use of sulfanilamide therapy. This was contrary to the usual findings. It is of further interest to observe that there was no capsular swelling in vivo of the pneumococci either during life or post mortem, despite the use of antipneumococcus rabbit serum. In a case recently observed by the authors, this *Quellung* phenomenon within the spinal fluid following the use of intravenous specific rabbit serum was observed. The *modus operandi* of the disease in this case may be postulated as follows: An infection of the right middle ear was followed by septicemia, and this, in turn, by meningitis. The pulmonary lesions were of recent origin, and the edema may be ascribed to an anaphylactic phenomenon. The circulatory collapse may again be considered an anaphylactic phenomenon with the pneumococcus toxin as the *inciting factor*. The organisms in positive cultures of the lungs were most probably of circulatory rather than parenchymal origin, as pneumococci rarely invade the parenchyma of the lung by way of the blood stream. The mechanism of production of pneumococcic pneumonia is at variance with an origin in the blood stream. The length of the disease process in this case confirms the theory of noncirculatory origin.

COMMENT

When this patient with type XIX pneumococcus meningitis entered the hospital a hasty search of the literature was made for a guide to therapeutic measures. Since sulfapyridine had proved so much superior to sulfanilamide in the treatment of pneumococcic pneumonia, it was assumed that the former drug would be the most effective against pneumococcic meningitis. Toomey and Roach³ and Long, Haviland, Edwards and Bliss⁶ all expressed such an assumption. However, a more extensive perusal of the literature suggested that there had been a higher percentage of recoveries attributable to sulfanilamide and azo derivatives. This review, which includes a summary of the cases of all the 48 patients treated with sulfanilamide and azo derivatives and the 67 patients treated with sulfapyridine reported in the literature to date, is made with the view of statistically determining the comparative efficacy of the two types of drug.

The summary at the end of table 3 shows that 68.75 per cent (33) recovered and 31.25 per cent (15) died of a total of 48 patients treated with sulfanilamide and azo derivatives, whereas only 53.7 per cent (36) recovered and 46.2 per cent (31) died of a total of 67 patients treated with sulfapyridine. If all patients who died during the first twenty-four hours are excluded (which probably should be done, since chemotherapy can hardly be expected to bring about a cure in less than

6. Long, P. H.; Haviland, J. W.; Edwards, L. B., and Bliss, E. A.: Clinical Evaluation of the Use of Sulfanilamide, Neoprontosil, Sulfapyridine and Sulfathiazole in the Treatment of Infections, *Mississippi Doctor* 17:541 (March) 1940.

twenty-four hours), the percentage of recoveries among patients treated with sulfanilamide and azo derivatives becomes 71 as contrasted with a percentage of 62.7 among those treated with sulfapyridine.

As the beneficial action of sulfanilamide against the type III pneumococcus has been demonstrated experimentally by Rosenthal, Bauer and Branham⁷ and Cooper, Gross and Mellon⁸ and clinically by Louis,⁹ Millett¹⁰ and Heintzelman, Hadley and Mellon,¹¹ it would seem important to determine whether or not the high total recovery rate with such an agent was in part the result of a higher effectiveness of sulfanilamide against the type III pneumococcus. Inspection of table 3 will show that this is not the case; for only 8 of the 17 patients with type III pneumococcus meningitis treated with sulfanilamide and azo derivatives recovered, while 5 of the 6 patients with type III pneumococcus meningitis treated with sulfapyridine recovered.

Definite conclusions pertaining to the relative effectiveness of the drug under consideration for therapy of the other types of pneumococcic meningitis is unwarranted because of the small number of case reports available for each.

The use of antipneumococcus serum in conjunction with chemotherapy appears to be of doubtful value, as the data in table 4 indicate that only 69 per cent of patients receiving this combination recovered. Nevertheless, despite this inability to demonstrate statistically that the recovery rate was significantly affected by the addition of type-specific serum, certain experimental and clinical evidence has been presented to show that the combination may on occasion be of greater value than chemotherapy alone. Branham and Rosenthal¹² found that the curative

7. Rosenthal, S. M.: Studies in Chemotherapy: The Effect of P-Aminobenzene Sulfonamide on Pneumococci in Vitro, *Pub. Health Rep.* **52**:192 (Feb. 12) 1937; Studies in Chemotherapy: Chemotherapy of Experimental Pneumococcus Infections, *ibid.* **52**:48 (Jan. 8) 1937. Rosenthal, S. M.; Bauer, H., and Branham, S. E.: Studies in Chemotherapy: Comparative Studies of Sulfonamide Compounds in Experimental Pneumococcus, Streptococcus and Meningococcus Infections, *ibid.* **52**:662 (May 21) 1937.

8. Cooper, F. B.; Gross, P., and Mellon, R. R.: Action of P-Aminobenzene Sulfonamide on Type III Pneumococcus Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **36**:148 (March) 1937.

9. Louis, D. J.: Treatment of Pneumonias with Sulfanilamide, *Illinois M. J.* **73**:422 (May) 1938.

10. Millett, J.: Sulphanilamide: Report of a Case, *New York State J. Med.* **37**:1743 (Oct. 15) 1937.

11. Heintzelman, J. H. L.; Hadley, P. B., and Mellon, R. R.: Use of P-aminobenzenesulphonamide in Type 3 Pneumococcus Pneumonia, *Am. J. M. Sc.* **193**:759 (June) 1937.

12. Branham, S. E., and Rosenthal, S. M.: Studies in Chemotherapy: Sulfanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, *Pub. Health Rep.* **52**:685 (May 28) 1937.

effect was greater when serum and sulfanilamide were combined than it was when either of these two substances was used alone. Finland, Brown and Rauh⁵ have recommended the combination of antipneumococcus serum and sulfanilamide and have pointed out that this combination has more effectively controlled massive infections of the blood stream. Cutts, Gregory and West¹³ treated a patient for two weeks with sulfapyridine alone, but despite clinical improvement the cultures of spinal fluid did not become negative until antipneumococcus rabbit serum was administered intravenously and complement intrathecally. McKay and Hurteau¹⁴ observed that a more rapid and complete response was obtained when specific serum was used in addition to sulfapyridine and that the low levels of sulfapyridine in the blood of patients receiving serum were not accompanied by exacerbations of the disease as they were in the absence of serum. Furthermore, physicians are in general agreement that type-specific antipneumococcus serum should be administered in addition to sulfapyridine when patients with pneumococcic pneumonia have bacteremia or have failed to respond to chemotherapy alone.

The evidence just presented would suggest that large doses of antipneumococcus rabbit serum are indicated in the presence of bacteremia or when the cultures of spinal fluid remain positive after the first twenty-four hours of chemotherapy or when the patient fails to respond to chemotherapy alone. Intrathecal administration of antipneumococcus horse or rabbit serum should be used only as a last resort because of the danger from severe allergic and foreign protein reactions. Intravenous injections of large doses of type-specific antipneumococcus rabbit serum followed by intrathecal administration of antibody in the form of complement (patient's own serum), as suggested by Finland, Brown and Rauh⁵ and others, appears effective and safer.

Pneumococcus antibodies are not produced during the first two years of life, and this may account at least in part for the fact that all babies under 2 years of age with pneumococcic meningitis died, regardless of the form of therapy administered. Thereafter, the recovery rate does not appear to have been appreciably influenced by the age of the patient. No conclusions can be drawn, however, concerning the effect of advanced age on the recovery rate as there was only 1 patient in this series over 60. The mortality rate was higher regardless of the form of therapy administered in the presence of bacteremia.

Table 1 shows that data concerning actual concentration of sulfanilamide or an azo derivative in the spinal fluid is lacking in such a large

13. Cutts, M.; Gregory, K. K., and West, E. J.: *Pneumococcus Meningitis Successfully Treated with Sulfapyridine*, J. A. M. A. **112**:1456 (April 15) 1939.

14. McKay, F. H., and Hurteau, E. F.: *Four Cases of Pneumococcus Meningitis Treated with Sulfapyridine*, Canad. M. A. J. **42**:463 (May) 1940.

number of the cases reported that it is impossible to draw any conclusions concerning the optimal level. It has been shown by investigators¹⁵ that the level of sulfanilamide in the spinal fluid is only slightly less than that in the blood, the minimal level in the latter being 8 to 10 mg. per hundred cubic centimeters.

The blood and the spinal fluid levels for sulfapyridine have been included for a larger number of the cases reported in table 2. In general the concentration of the drug in the spinal fluid appears to average about one-half to three-quarters that in the blood stream. Clinicians¹⁶ have demonstrated the variability in the absorption rate of sulfapyridine from the intestinal tract and the rate of excretion from the kidneys in different persons and have attributed some of their failures to obtain recovery to the resultant low levels of the drug in the blood and spinal fluid. Failure of our patient to recover may be a case in point. It seems fairly well agreed that the concentration of free sulfapyridine in the spinal fluid should be maintained at 5 to 8 mg. or more per hundred cubic centimeters.¹⁷ Some authors¹⁸ have suggested that sodium sulfapyridine be administered intravenously or intramuscularly to all patients that have a low blood and spinal fluid concentration of the drug after its oral administration. In view of the importance of speed in many cases and the difficulty in oral administration due to comatose states and other causes, it seems highly probable that sodium sulfapyridine may well become the drug of choice if sulfapyridine drugs are to continue in use. However, evaluation of the relative effectiveness of sodium sulfapyridine must await its use in a larger series of cases.

It is entirely possible that the cases thus far reported in the literature may not represent a true cross section of the effectiveness of the drugs

15. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Paraaminobenzenesulfonamide; Absorption and Excretion: Method of Determination in Urine and Blood, *J. A. M. A.* **108**:951 (March 20) 1937. Banks, S.: Serum and Sulfanilamide in Acute Meningococcal Meningitis, *Lancet* **2**:7 (July 2) 1938. Allott, E. N.: Sulfanilamide Content of Cerebro-Spinal Fluid, *ibid.* **2**:13 (July 2) 1938. Long, P. H., and Bliss, E. A.: The Use of Para-Amino-Benzene-Sulfonamide (Sulfanilamide) or Its Derivatives in the Treatment of Infections Due to Beta Hemolytic Streptococci, Pneumococci, and Meningococci, *South. M. J.* **30**:479 (May) 1937.

16. (a) Hodes, H. L.; Gimble, H. S., and Burnett, G. W.: Pneumococcic Meningitis, *J. A. M. A.* **113**:1614 (Oct. 28) 1939. (b) Long, Haviland, Edwards and Bliss.⁶

17. (a) Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases, *Arch. Int. Med.* **65**:671 (April) 1940. (b) Hodes, Gimble and Burnett.^{16a}

18. (a) Cable, J. V.: Pneumococcus Meningitis: A Review of Thirty-Nine Fatal Cases and a Report of Recovery After Administration of M. & B. Soluble, *Lancet* **2**:73 (July 8) 1939. (b) Hodes, Gimble and Burnett.^{16a} (c) Falla, S. T.: Treatment of Pneumococcus Meningitis with Sulfapyridine, *Brit. M. J.* **1**:804 (May 18) 1940. (d) Kolmer.^{17a}

under consideration, for it may well be that many individual failures have not been reported in the literature. It is a human tendency to report successes. We suggest that a central bureau might be established to collect and correlate the data on future cases of pneumococcic meningitis treated by chemotherapy, for we feel that each hospital would be willing to cooperate to the extent of filling out special forms regarding cases of this disease in which such treatment was given.

Postmortem findings should be recorded whenever possible. In our case an interesting finding was that of cerebral thrombosis. Lyons¹⁹ has found similar evidence in some of his fatal cases and attributed failure to recover to this complication. With this in view he recommends the administration of heparin in conjunction with chemotherapy when thrombosis is suspected clinically.

SUMMARY

A case of type XIX pneumococcus meningitis treated with sulfapyridine and type specific serum with failure to recover is reported.

An observation of capsular swelling in the pneumococci withdrawn in the spinal fluid after the intravenous administration of type XVIII antipneumococcus rabbit serum is recorded.

In comparable series of reported cases sulfanilamide an azo derivative has been as effective as sulfapyridine in the treatment of pneumococcic meningitis.

Sulfapyridine was more effective than sulfanilamide and azo derivatives in the treatment of type III pneumococcus meningitis.

The use of type-specific antipneumococcus serum in conjunction with chemotherapy has not materially lowered the mortality rate of pneumococcic meningitis.

The mortality rate regardless of the form of therapy has been 100 per cent for patients under 2 years of age.

The mortality rate regardless of the form of treatment was higher whenever there was an associated bacteremia.

The concentration of sulfanilamide in the blood should be kept up to 10 mg. or more per hundred cubic centimeters.

More observations are necessary to determine the optimal concentration of sulfanilamide in the spinal fluid. It probably is 8 or 10 mg. per hundred cubic centimeters.

Levels of sulfapyridine in the blood and the spinal fluid should be maintained at 10 mg. or more and 5 mg. or more per hundred cubic centimeters, respectively.

19. Lyons, C.: Personal communication to the authors.

Absorption of sulfapyridine from the gastrointestinal tract and the rate of excretion from the kidneys are extremely variable and this is believed to account for some of the wide variations in the concentration of the drug in the blood and the spinal fluid.

Oral administration of sulfapyridine should be augmented or replaced by intravenous or intramuscular administration of sodium sulfapyridine whenever the concentration of the drug in the blood and the spinal fluid remains low.

Since sulfanilamide is a safer drug, is more readily and uniformly absorbed and, as table 4 indicates, is as effective as sulfapyridine or sodium sulfapyridine in the treatment of pneumococcic meningitis, its use should be continued as one of the forms of chemotherapy until such time as either of the last-named drugs has been shown to be definitely superior.

The use of chemotherapeutic agents has reduced the mortality of pneumococcic meningitis from 100 to approximately 33.3 per cent.

Ruth French Swift prepared the tables and did the bibliographic research for this paper.

ORIGIN OF BLOOD AMYLASE AND BLOOD LIPASE IN THE DOG

RELATION BETWEEN BLOOD AMYLASE AND URINARY AMYLASE FOLLOWING INDUCTION OF URANIUM NEPHRITIS

DANIEL L. DOZZI, M.D.

PHILADELPHIA

In another communication ¹ I discussed the current views concerning the origin of blood amylase, cited the experimental data from the literature in support of the theory that blood amylase is entirely of pancreatic origin and presented the concepts of those who have expressed the belief that blood amylase is, in part at least, of hepatic origin. Although it has been the general experience of most workers that chloroform anesthesia induces a fall in blood amylase, there is some difference of opinion as to whether this result is due to the effect of chloroform on the liver or its effect on the pancreas. Davis and Ross ² reported that they were unable to induce a drop in blood amylase by administering chloroform to depancreatized dogs and inferred that the reduction in blood amylase is due to the effect of chloroform on the pancreas. Cajori and Vars, ³ on the other hand, found that the decrease in serum amylase following chloroform anesthesia was greatest in those dogs whose livers contained areas of necrosis.

Just as there is a difference of opinion concerning the origin of amylase, there are conflicting data concerning the relation between blood amylase and urinary amylase both in normal and in pathologic states. Gray and Somogyi ⁴ reported that in any person the level of blood amylase remains fairly constant, while the value for urinary amylase varies greatly and irregularly. However, despite such variation, they found a definite relation between the amount of amylase in the blood and the amount in the urine, in that the proportion of urinary amylase

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1. Dozzi, D. L.: Urinary Amylase: Its Estimation and Significance, *Am. J. Digest. Dis.* **7**:123, 1940.

2. Davis, L. H., and Ross, E. L.: The Source of Diastase of the Blood, *Am. J. Physiol.* **56**:22, 1921.

3. Cajori, F. A., and Vars, H. M.: The Effect of Chloroform Anesthesia on Serum Amylase and Liver Esterase, *Am. J. Physiol.* **124**:149, 1938.

4. Gray, S. H., and Somogyi, M.: Relationship Between Blood Amylase and Urinary Amylase in Man, *Proc. Soc. Exper. Biol. & Med.* **36**:253, 1937.

to blood amylase varies between 2:1 and 6:1. Nørby⁵ stated that the excretion of amylase in the urine is proportional to the concentration of the enzyme in the serum. Geyelin⁶ reported that the amount of amylase in twenty-four hour specimens of urine varies little for the normal person and in a given case is almost constant. My own experience¹ revealed great fluctuation for the same person, as well as from person to person, in the amount of amylase excreted in the urine during twenty-four hour periods.

Wohlgemuth,⁷ Corbett,⁸ Geyelin,⁶ Fitz,⁹ Rowntree, Marshall and Baetjer,¹⁰ Fearon,¹¹ Gray and Somogyi⁴ and others have reported finding a decrease in urinary amylase in the presence of nephritis. Gray and Somogyi⁴ stated that if the blood amylase is elevated, the level of urinary amylase must be determined, in order to conclude whether the rise of the enzyme in the blood is due to increased formation or merely to renal retention.

In support of the view that an elevation in the blood amylase, due to retention, is associated with renal impairment, one can cite the work of Meyer and Killian,¹² Harrison and Lawrence,¹³ Brill,¹⁴ Reid,¹⁵ Gelera,¹⁶ Gray and Somogyi⁴ and others. On the other hand, Stafford

5. Nørby, G.: Om amylasen blod og urin—dens udskillelse gennem nyren, Copenhagen, Levin & Munksgaard, 1935; reviewed, *J. A. M. A.* **108**:1996 (June 5) 1937.

6. Geyelin, H. R.: A Clinical Study of Amylase in the Urine, *Arch. Int. Med.* **13**:96 (Jan.) 1914.

7. Wohlgemuth, J.: Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments, *Biochem. Ztschr.* **9**:1, 1908.

8. Corbett, D.: The Quantitative Estimation of Amylolytic Ferments in the Urine as a Measure of Certain Pathological Conditions, *Quart. J. Med.* **6**:351, 1912.

9. Fitz, R.: The Relation Between Amylase Retention and Excretion and Non-Protein Nitrogen Retention in Experimental Uranium Nephritis, *Arch. Int. Med.* **15**:524 (April) 1915.

10. Rowntree, L. G.; Marshall, E. K., Jr., and Baetjer, W. A.: Further Studies of Renal Function in Renal, Cardioresenal and Cardiac Diseases, *Arch. Int. Med.* **15**:543 (April) 1915.

11. Fearon, W. R.: The Amylolytic Properties of Urine and the Significance of Variations in Health and Disease, *Dublin J. M. Sc.* **146**:149, 1918.

12. Meyer, V. C., and Killian, J. A.: The Increased Diastatic Activity of the Blood in Diabetes and Nephritis, *J. Biol. Chem.* **29**:179, 1917.

13. Harrison, G. A., and Lawrence, R. D.: Diastase in Blood and Urine as a Measure of Renal Efficiency, *Lancet* **1**:169, 1923.

14. Brill, I. C.: Studies in the Diastatic Activity of the Blood with a Consideration of Its Value in Clinical Diagnosis, *Arch. Int. Med.* **34**:542 (Oct.) 1924.

15. Reid, C.: Diastatic Activity in Blood and Urine, *Brit. J. Exper. Path.* **6**:314, 1925.

16. Gelera, M.: La diatasemia da ritenzione quale prova funzionale del rene, *Folia med.* **14**:630, 1928.

and Addis¹⁷ failed to find a relation between the extent of the renal lesion in patients with Bright's disease and the concentration of diastase in plasma or urine or the rate of diastase excretion. Moreover, they could not correlate the amounts of nonprotein nitrogen and amylase in the blood. I¹ was unable to relate the amount of amylase in twenty-four hour specimens of urine to the extent of renal impairment as determined by the level of nonprotein nitrogen in the blood and the amount of urea excreted.

Rowntree and his co-workers¹⁰ studied the quantitative determination of urinary amylase as a test of renal function and found that while the level of urinary amylase usually decreased in cases of nephritis, values were normal in cases of grave functional involvement and low in cases in which there was improvement of renal function. Fitz⁹ reported a direct relation between the levels of nonprotein nitrogen and amylase in the blood with reference to the severity of renal disease, and Geyelin⁶ found parallelism between the amounts of phenolsulfonphthalein and amylase which were excreted.

The difference of opinion concerning both the origin of amylase and the relation between the amounts of enzyme in blood and urine, stimulated my interest in an attempt to determine (a) whether blood amylase is solely pancreatic in origin or in part, at least, hepatic and (b) what relation exists between the levels of blood and urinary amylase, particularly in the presence of nephritis.

BLOOD AMYLASE AND URINARY AMYLASE

Procedure.—Five healthy female dogs were maintained on the same diet throughout the experiment, and estimations of the normal levels of blood and urinary amylase were performed by a colorimetric, a saccharogenic and a viscosometric method, all of which have been described in another paper.¹⁸ Because the saccharogenic method proved to be the most accurate, I am reporting only the results which were obtained by that method, although all three were used simultaneously. After normal values were determined for all 5 animals, 2 dogs were subjected to complete pancreatectomy and 2 to partial pancreatectomy. After the effect of depancreatization on the levels of amylase in the blood and urine had been determined, the animals were subjected to chloroform anesthesia, and the blood and urinary amylase were again studied. The fifth dog was given increasing doses of uranium nitrate through a stomach tube, and the levels of blood and urinary amylase were studied in conjunction with determination of the nonprotein nitrogen of the blood and repeated urinalyses. When definite nephritis had been produced by the uranium, as evidenced by polyuria, glycosuria, albuminuria and increase in the nonprotein nitrogen of the blood, the dog was anesthetized with ether and the pancreatic ducts were ligated in an attempt to determine whether the suddenly

17. Stafford, D. D., and Addis, T.: *Diastase Determinations in Urine and Blood as a Method for Measurement of Functional Capacity of Kidney*, Quart. J. Med. **17**:151, 1924.

18. Dozzi, D. L.: *An Evaluation of Methods for Determining Blood and Urinary Amylase*, J. Lab. & Clin. Med. **25**:1303, 1940.

increased amount of amylase in the blood, resulting from the ligation, would be excreted by the nephritic kidneys.

Results.—The normal values for the 5 dogs show that no relation existed between the amount of amylase in the blood and the amount in

TABLE 1.—*Variations in Blood and Urinary Amylase Following Complete Pancreatectomy and Chloroform Anesthesia*

Day of Experiment	Blood Amylase *	Urinary Amylase †	Procedure	Blood Urea			Urinalysis	Blood Lipase ‡
				Urine, Cc. per 24 Hr.	Nitrogen, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.		
Dog 344; weight, 10 Kg.								
1	580	53	Dog normal	221	11	0.2	Urine normal	1.15
4	640	None	160	0.55
8	1,360	750	124	0.10
11	560	29	152	1.00
14	Chloroform anesthesia (1 hour)
15	40	71	278	1.00
16	380	56	197	..	0.6	1.05
17	220	7	240	..	1.0	1.05
18	1,040	None	175	..	0.4	1.00
21	660	None	75
22	Complete pancreatectomy
23	640	None	0.2	1.05
24	820	None	170	1.70
25	560	...	Chloroform anesthesia (½ hour)§
26
27	520	...	Natural death	0.5	0.60
Dog 715; Weight, 11.5 Kg.								
1	126	No determination	Dog normal
7	150	...	Complete pancreatectomy §
8	44
11	76
12	66
14	48	...	Chloroform anesthesia (½ hour)§
8 hr. later	52	...	Natural death

The following symbols have the same significance in tables 2 and 3.

* The amount of amylase in the blood is expressed in terms of milligrams of dextrose formed from the hydrolysis of starch solution by 100 cc. of serum.

† The amount of amylase in the urine is expressed in terms of milligrams of dextrose formed from the hydrolysis of starch solution by a twenty-four hour specimen of urine.

‡ The amount of lipase in the blood is expressed in terms of cubic centimeters of a twentieth-normal solution of sodium hydroxide required to neutralize the fatty acids liberated by the action of 1 cc. of serum on an olive oil emulsion.

§ Enzyme studies were performed prior to the procedure.

the urine. Four dogs showed appreciable quantities in the blood, with practically none in the urine. Comparatively large quantities occurred both in the blood and in the urine of the fifth dog. Because of the high level of urinary amylase, the last dog was subjected to the administration of uranium nitrate in order to determine whether a diminution in the urinary amylase would follow the induction of nephritis.

In table 1 are recorded the data for the 2 dogs subjected to complete pancreatectomy. That the entire pancreas was removed is supported

both by the onset of diabetes and by the absence of pancreatic tissue at autopsy. In 1 animal the level of blood amylase was not appreciably affected by complete pancreatectomy, while in the other there was a distinct drop. One dog died twenty-four hours and the other eight hours after thirty minutes of chloroform anesthesia. The blood amylase was studied prior to death and showed no apparent change from normal.

TABLE 2.—*Variations in Blood and Urinary Amylase Following Partial Pancreatectomy and Chloroform Anesthesia*

Day of Experiment	Blood Amylase *	Urinary Amylase †	Procedure	Blood Urea			Urinalysis	Blood Lipase ‡
				Urine, Cc. per 24 Hr.	Nitrogen, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.		
Dog 336; Weight, 16.4 Kg.								
1	740	None	Dog normal	192	10	...	Urine normal	0.85
4	920	226	0.30
8	1,040	190
11	1,000	213	..	0.2	0.55
30	Partial pan- createctomy					
31	1,040	227	170	3.35
32	2,040	None	140	3.80
33	1,220	3.50
35	920	...	Chloroform anes- thesia (1 hr.)§	2.50
36	660	0.8	2.00
37	620	2.0	2.40
38	620	200	..	3.0	2.30
39	820	1,000	..	2.0	1.60
40	500	350	1.30
44	630	...	Chloroform anes- thesia (1 hr.)§	0.65
46	200	1.0	1.15
47	300	2.4	0.90
50	660	...	Chloroform anes- thesia (1 hr.)§	0.3	1.10
52	180	...	Dog killed	2.0	0.80
Dog 656; Weight, 12.9 Kg.								
1	130	None	Dog normal	0.1
3	140
4	214	...	Partial pan- createctomy §					
5	272
8	232	...	Chloroform anes- thesia (1 hr.)§					
10	146	...	Dog killed					

Since Cajori and Vars³ found that the maximum effect on the serum amylase following chloroform anesthesia does not occur until twenty-four to forty-eight hours later, I feel that no conclusions can be drawn from this experiment.

Two dogs were partially depancreatized, only a remnant, approximately 2.5 by 1.5 by 1.5 cm., being left intact. In both animals a partial, temporary rise in the blood amylase following pancreatectomy was succeeded by a distinct drop after the administration of chloroform. One animal was anesthetized with chloroform three different times, with the same result, a reduction in serum amylase and an increase in serum bilirubin (table 2; fig. 1). After the third time the animal was in

extremely poor condition and was killed. The microscopic slides of the liver showed areas of necrosis, cellular infiltration and cloudy swelling, while the histologic picture of the pancreatic remnant was essentially normal. It would appear from these findings that the liver plays some part in the formation of amylase.

The results of the findings in the dog with nephritis are shown in table 3 and figure 2. It will be noted that an increase in the amount of amylase in the succeeding twenty-four hour specimen of urine followed each increase in the dose of uranium nitrate. The blood amylase remained fairly constant, with a tendency to diminish as the urinary amylase increased. The greatest total excretion of amylase per twenty-four hours occurred as the severity of the nephritis and the level of non-

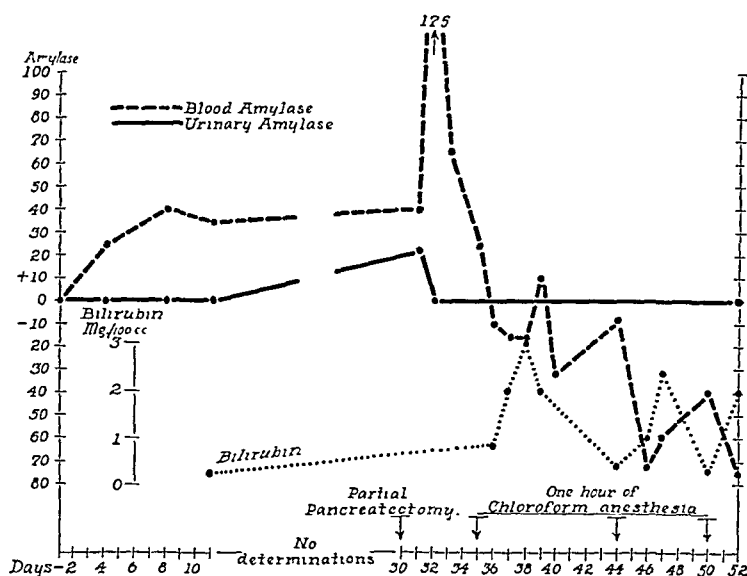


Fig. 1.—Relation of blood and urinary amylase in a dog submitted to partial pancreatectomy and chloroform anesthesia. Determinations of both blood and urinary amylase were made before the anesthesia was induced. In this figure and in figure 2, amylase is expressed in terms of milligrams of dextrose formed from the hydrolysis of starch solution by 100 cc. of serum, or by a twenty-four hour specimen of urine.

protein nitrogen in the blood increased, although excretion per unit of urine was lower because of polyuria. After ligation of the pancreatic ducts both blood and urinary amylase increased considerably, but the rise in the latter was out of all proportion to the increase in the former. It would appear from these results that no definite relation exists between the amount of amylase in the blood and the amount in the urine and that kidneys damaged by uranium nitrate excrete amylase more readily than do normal kidneys.

The finding of an increased amount of amylase in the urine in the presence of uranium nephritis is not in accord with the results of most

investigators. However, both Geyelin⁶ and Corbett⁸ noted an increase in urinary amylase in association with large quantities of albumin, even though they reported a decrease in urinary amylase in cases of nephritis. Both authors commented that they were uncertain whether the amount of amylase increased in the presence of albumin or whether the albumin merely accelerated amylolytic activity. The largest quantities of amylase in the urine of the nephritic dog herein described were also found when albumin was present. If amylase is of the nature of a protein, one wonders if there should not be more amylase in the urine when albumin is escaping from the kidney.

TABLE 3.—*Variations in Blood and Urinary Amylase Following Induction of Uranium Nephritis and Ligation of the Pancreatic Ducts*

Day of Experiment	Blood Amylase *	Urinary Amylase †	Procedure	Blood Urea			Urinalysis	Blood Lipase ‡
				Urine, Cc. per 24 Hr.	Nitrogen, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.		
Dog 411; Weight, 13.4 Kg.								
1	2,280	524	Dog normal	350	14.0	0.2	Urine normal	6.15
2	2,736	1,572	290	9.80
3	2,280	524	400	9.80
6	26 mg. uranium nitrate
7	1,340	2,024	280	16.0	4.50
8	2,240	8,614	135	17.6	...	Albumin ++	7.30
9	3,140	1,503	244	17.4	9.00
10	80 mg. uranium nitrate
				660	36.0	...	Albumin ++	7.00
15	1,720	3,045	875	21.0	...	Sugar ++	5.50
16	1,280	1,287	370	14.0	...	Albumin +	5.20
17	1,100	400	430	3.20
17	160 mg. uranium nitrate §
21	1,620	3,891	380	11.0	4.20
23	1,620	4,328	890	31.0	...	Sugar ++	6.00
25	840	1,139	1,700	22.0	...	Albumin ++	6.00
27	Ligation of pancreatic ducts
28	6,240	5,370	1,500	18.0	...	Albumin +++	13.50
29	3,880	9,600	1,000	13.0	...	Albumin +++	16.00
30	3,680	3,304	530	11.40
31	3,220	3,304	530	11.80
			Dog killed	500	12.20

SERUM LIPASE

In conjunction with the studies on amylase, the serum lipase was determined, according to the method described by Cherry and Crandall,¹⁹ for 1 of the completely depancreatized dogs, in 1 of the partially depancreatized dogs and the dog with uranium nephritis. The results are included in tables 1, 2 and 3.

In dog 344 (table 1) chloroform given prior to pancreatectomy had no effect on the serum lipase, although there was a distinct drop in the

19. Cherry, I. S., and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood After Pancreatic Injury, *Am. J. Physiol.* **100**:266, 1932.

serum amylase. After complete pancreatectomy the serum lipase gradually diminished, while the serum amylase remained approximately the same.

In dog 336 (table 2) both serum lipase and serum amylase increased after partial pancreatectomy and steadily decreased after repeated chloroform anesthesia.

In dog 411 (table 3) both the serum lipase and the serum amylase were elevated prior to the administration of uranium nitrate. After the induction of nephritis, the serum lipase was not appreciably effected,

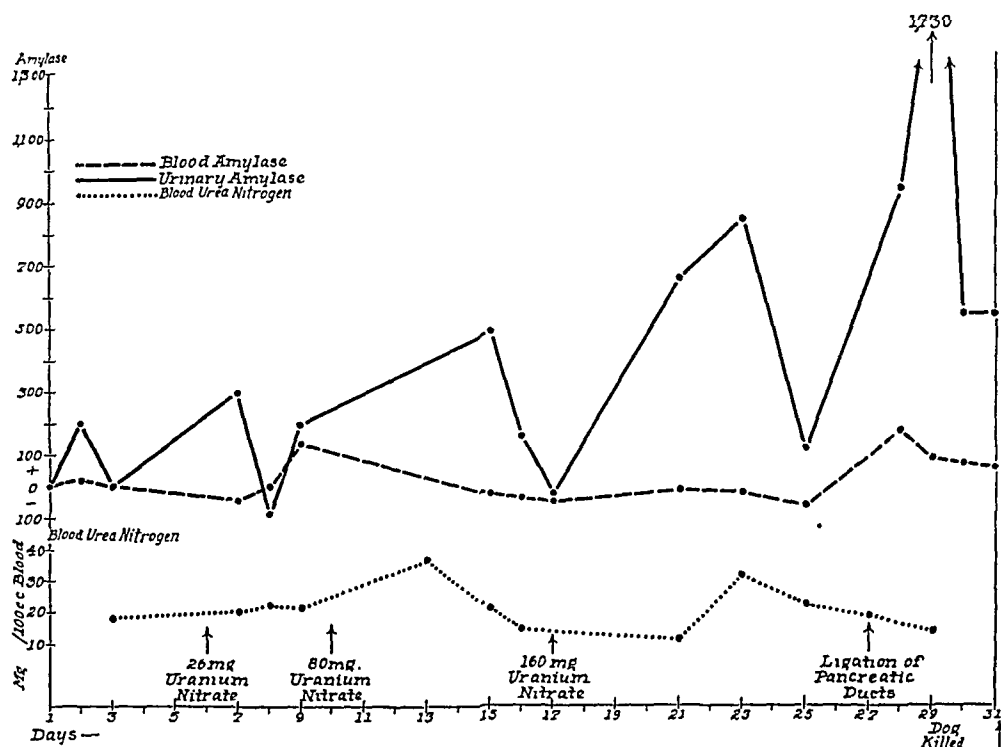


Fig. 2.—Relation of blood and urinary amylase in dog with uranium nephritis.

while the serum amylase tended to decline. After ligation of the pancreatic ducts, both serum lipase and serum amylase were elevated.

The relative stability of serum lipase levels following chloroform anesthesia and the steady decrease following complete pancreatectomy would indicate that lipase is more apt to be entirely of pancreatic origin than is amylase. The failure of serum lipase to decrease or increase after the induction of nephritis would indicate that the level of this enzyme in the serum is not dependent on renal function.

SUMMARY

Blood amylase and urinary amylase were studied in 2 completely depancreatized dogs, 2 partially depancreatized dogs and 1 dog with uranium nephritis. The effects of chloroform anesthesia and ligation of

the pancreatic ducts were observed. Some studies of the serum lipase were performed coincident to those on amylase. The following conclusions are drawn:

1. A definite relation seems to exist between the degree of hepatic damage and the amount of amylase in the serum, which indicates that the liver plays some part, at least, in the formation of amylase.

2. There is no demonstrable relation between the amount of amylase in the urine and the amount in the blood.

3. In the presence of uranum nephritis in the dog the urinary amylase increases, while the serum amylase tends to decrease.

4. The level of serum lipase does not appear to be affected by chloroform anesthesia, but its steady diminution after complete pancreatectomy indicates that serum lipase is more truly of pancreatic origin.

5. The level of serum lipase does not depend on renal function.

Dr. I. S. Ravdin performed the operations, and Dr. F. A. Cajori and Dr. Harry M. Vars contributed many helpful suggestions.

CLINICAL AND PHYSIOLOGIC CHARACTERISTICS OF CHILL

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To both physician and layman, a chill represents a serious and alarming sign. A combination of both subjective and objective bodily changes, varying in intensity from a tremulous feeling or a sensation of cold to a violent, widespread shivering or rigor, a chill may involve part of the body or its entirety and may be due to external or internal causes (e. g., exposure to cold or bacterial invasion).

With the realization that no clearcut separation can therefore be made, the word "chill" will be applied to the combination of a subjective perception of inward trembling or actual cold and a more or less generalized involuntary muscle tremor visible as an objective sign. Such a definition, first given by Richet ¹ almost fifty years ago, does not include the lesser degrees of transitory shivering, chilliness or sensations of cold, which may all be due to similar causes and mechanisms, but it has the advantage that it places the clinical significant type of reaction in a distinct group and allows more accurate methods of study.

Chills are mentioned in the earliest medical writings. Hippocrates spoke of the rigors associated with consumption, and throughout the course of medical and literary history one finds frequent reference to this sign of disease. "Ague"—signifying recurrent chills and fever such as exist in malaria—was a popular word several centuries ago. Despite their frequency and importance, only in recent years have chills been studied along the same physiologic lines as other manifestations of illness. Dworkin, in 1930, wrote: "Apart from [the chill's] influence on heat regulation . . . very little is known concerning its mode of origin and its nervous control." ²

In this paper I shall report certain clinical and experimental observations dealing only with chills in their relation to human disease, reviewing the literature and utilizing previous researches on the shivering that may follow exposure to cold and on artificially produced chills as an

From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

1. Richet, C.: (a) *Le frisson comme appareil de régulation thermique*, Compt. rend. Soc. de biol. **44**:896, 1892; (b) *Arch. de physiol. norm. et path.* **25**:312, 1893.

2. Dworkin, S.: *Observations on the Central Control of Shivering and of Heat Regulation in the Rabbit*, Am. J. Physiol. **93**:227 (May) 1930.

additional means for comparison and study of the mechanisms involved. Richet¹ divided chills into three categories: toxic, occurring with infections or after intravenous injections; psychic, following fright, and environmental, due to reduction of the external temperature.

One can only surmise as to the function of chills in disease. Shivering is an important mechanism in temperature regulation, serving to increase heat production when an external factor for increased heat loss has been introduced (Fredericq³; Hardy, Milhorat and Du Bois,⁴ and Müller⁵). On less established ground one may conclude from the supportive observations by Bazett,⁶ Bazett and Penfield⁷ and Clark, Magoun and Ranson⁸ that when shivering is absent the ability to withstand a rapid fall in environmental temperature by increased heat production is also lost. Modern teachers speak of a central "thermostat" set to a higher level by a toxic agent, with the shivering response as a means of raising body temperature to its new reading. Such teleologic reasoning still lies in the realm of pure speculation.

Chills may be seen in any infectious process, whether produced by bacterium, virus, parasite or toxin, but particularly in the course of rapid and widespread invasion of the host. The following observations are evidence that such invasion directly stimulates the shivering mechanism: Schottmüller⁹ claimed that chills followed but did not come directly after bacterial invasion; Delcourt-Bernard¹⁰ noted that chills appeared about fifty minutes after injections of vaccine; Petersen and Müller¹¹ produced chills by injection of sterile milk (aolan) intramuscularly, and shivering is frequent during artificial fever therapy with killed typhoid or malaria organisms.

3. Fredericq, L.: Sur la régulation de la température chez les animaux à sang chaud, *Arch. de biol.* **3**:687, 1882.

4. Hardy, J. D.; Milhorat, A. T., and Du Bois, E. F.: The Effect of Exercise and Chills on Heat Loss from the Nude Body, *J. Nutrition* **16**:477 (Nov.) 1938.

5. Müller, E. F.: Ueber den Schüttelfrost, *München. med. Wchnschr.* **73**:1349 (Aug. 13) 1926.

6. Bazett, H. C.: Further Experiments on Chronic Decerebrate Cats, *Am. J. Physiol.* **101**:5 (June) 1932.

7. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as Acute Condition, *Brain* **45**:185 (Oct.) 1922.

8. (a) Clark, G.; Magoun, H. W., and Ranson, S. W.: Hypothalamic Regulation of Body Temperature, *J. Neurophysiol.* **2**:61 (Jan.) 1939; Temperature Regulation in Cats with Thalamic Lesions, *ibid.* **2**:202 (May) 1939. (b) Ranson, S. W.: Some Functions of the Hypothalamus, in *Harvey Lectures 1936-1937*, Baltimore, Williams & Wilkins Company, 1937, p. 92.

9. Schottmüller, H.: Streptokokken-Aborte und ihre Behandlung, *München. med. Wchnschr.* **58**:2051 (Sept. 26) 1911.

10. Delcourt-Bernard, E.: L'accès fébrile chez l'homme, *Rev. belge sc. méd.* **5**:229 (April) 1933.

11. Petersen, W. F., and Müller, E. F.: Correlation of Skin and Stomach Tonus, *Proc. Soc. Exper. Biol. & Med.* **24**:155 (Nov.) 1926.

GENERAL CONSIDERATIONS

Incidence.—Out of 500 patients admitted consecutively to the medical and surgical services at the Peter Bent Brigham Hospital during the winter of 1940, 28 (5.6 per cent) had chills either in the course of the illness for which they were admitted or their stay in the hospital. Another consecutive series of 500 patients admitted during the summer of 1939 included only 12 (2.2 per cent) with chills as a part of their illness. The much higher incidence of acute infection and acute illness of the respiratory tract during the colder times of year is the probable explanation of this seasonal discrepancy.

I have observed chills in a child of 25 months and in a patient of 80 years. Talbot¹² did not describe chills in premature infants. He stated that only a few slight muscle movements follow exposure to cold. These, or convulsive movements, are the equivalent manifestations with disease in infancy.

Latent Period.—That a period elapses between the introduction of a causative agent and the onset of chill is implied by the following observations. In 10 patients recently treated by intravenous injection of typhoid vaccine and in another 10 who reacted after transfusion, chills appeared between forty and sixty-five minutes after the injection of the vaccine or the start of transfusion in every case. One patient was observed who had a chill one hour after an intravenous injection of physiologic solution of sodium chloride, subsequent cultures of which showed contamination by *Staphylococcus aureus*. Intramuscular injections of typhoid vaccine, sterile milk, etc., on the other hand, are apt to produce reactions only after several hours, occasionally with a mild chill at the onset.

Duration.—As Swift¹³ pointed out, it is often difficult to decide when a chill starts. In addition, the reports of the onset and the duration often depend on the patient's reliability or the presence of observers at the time a reaction begins. Furthermore, chills may be intermittent or may be modified by the treatment given. In my experience they may last from a few minutes to at least three hours. Of 35 patients seen during or soon after a chill, 25 stated that it lasted from fifteen minutes to one hour, and the remainder, from "just a few minutes" to three hours. The average duration (in hospital patients) was forty-three minutes.

Richet remarked that on exposure to cold, small, hairless dogs trembled more than large, fur-laden animals.¹ Swift noted that in a general way the reaction to cold varied inversely as the amount of subcutaneous

12. Talbot, F. B.: Skin Temperatures in Children, *Am. J. Dis. Child.* **42**:965 (Oct.) 1931.

13. Swift, R. W.: The Influence of Shivering, Subcutaneous Fat, and Skin Temperature on Heat Production, *J. Nutrition* **5**:227 (May) 1932.

fat.¹³ Similar results are found in the chill of disease. Plotting the weight of the patient against the duration of the chill revealed a relation in the majority of cases (chart 1). Another factor in the duration of chill is the height of the ensuing temperature peak. Again, a rough proportionality could be drawn among 29 patients whose temperature was recorded. As one might expect, the longer a heat-producing mechanism continues, the higher is the resultant body temperature (chart 2).

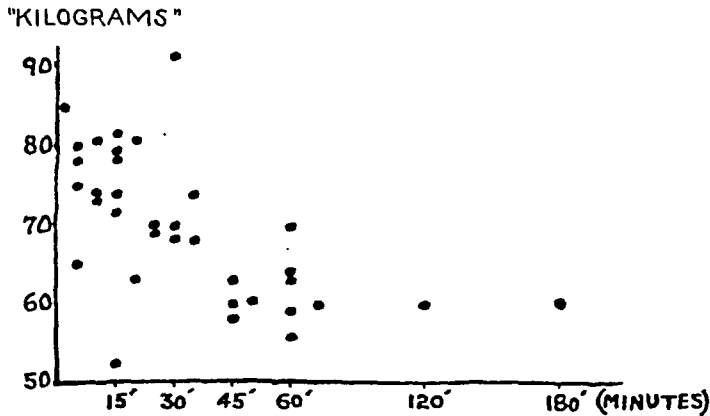


Chart 1.—Relation of body weight to duration of chill.

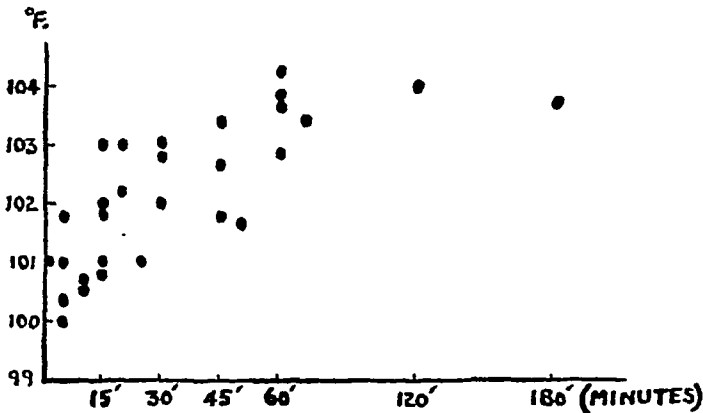


Chart 2.—Relation of duration of chill to ensuing temperature peak.

Intensity.—"If the bed shakes or the patient's teeth chatter, that's a chill." This statement serves to illustrate that greater significance is usually placed on chills of greatest severity. In general the intensity both of a chill and of the resultant febrile response is proportional to the dose of typhoid vaccine given intravenously for purposes of fever therapy. This observation and my own clinical experience point out that as a rule the more severe muscle tremors are associated with the more severe results after the chill is concluded. One must not draw conclusions too readily in any individual case; the amount of external covering, the

duration of the reaction, the degree of obesity, perhaps variations in the sensibility of the nervous system and other factors, all may be modifying influences.

A further cause of variation in intensity is the respiration. Richet was the first to note that chills were more marked during inspiration and were reduced during expiration¹; Magne¹⁴ made a similar comment. This was noted in 7 of 10 hospital patients observed while a chill was in progress, and the observers were able to make it apparent in the remaining 3 by having them take deeper breaths. A possible mechanism for this variation is suggested in the unrelated work of Mulinos and Shulman,¹⁵ who claimed that inspiration per se is associated with vasoconstriction.

SUBJECTIVE SYMPTOMS

Thirty-five patients were questioned during a chill or within forty-eight hours of its occurrence. Fourteen noted some sort of premonitory complaint before the actual onset of shaking. Ten of these spoke of a short period of antecedent fatigability or physical weakness; 9 described a sensation of "tenseness," "tightness" or "suspense"; headache developed in 5, and 3 felt nauseated, 1 of them vomiting just prior to the chill.

During the chill the perception of cold was usually unpleasantly apparent to all, but a few merely "felt trembly inside," at times even uncomfortably warm. One patient spontaneously remarked that his skin felt cold to the touch; another, that "I felt hot, but I was still shivering." The discomfort, however, tapered progressively in all, and as the body temperature rose, the majority had a relative sense of increasing warmth and unusual well-being, only to be replaced by the malaise and other symptoms of fever.

Most patients admitted to a centrifugal character to the chill. That is, they first or predominantly felt "cold shivers" down the back or coldness or tremulousness inside the chest or abdomen; the tremor of jaws or arms came involuntarily from the sensation of more deep-seated frigidity or quaking. Only a few persons, those whose chill was short or mild, claimed that their legs or arms felt coldest.

A desire for warmth was often expressed, and all who had access to blankets, more clothing or hot drinks or were able to curl up under the bedclothes with hot water bottles or electric pads, felt the better for it. Significant, however, were such statements as "I still couldn't stop shivering" and "I just couldn't get warm enough." Frequency of urination, with the passage of small amounts of pale urine, was commonly revealed when specific questions on this subject were asked the patient.

14. Magne, H.: La polypnée et le frisson thermiques, *Ann. de physiol.* **4**:650 (Nov.) 1928.

15. Mulinos, M. G., and Shulman, I.: Vasoconstriction in Hand from Deep Inspiration, *Am. J. Physiol.* **125**:310 (Feb.) 1939.

SIGNS

Temperature.—Chills and fever have been linked together for centuries, but it has remained for workers in recent years to understand their relation more accurately. Swift¹³ remarked on the absence of initial change in rectal temperature in chills produced by low environmental temperatures but found a drop in cutaneous temperature with the suggested threshold of 19 C. (66.2 F.) as the level at which shivering commences. Petersen and Müller¹⁶ observed that during chills of disease the cutaneous temperature falls while the rectal temperature begins an upward climb—at times preceded by an actual drop at the start of shivering.

Du Bois and his collaborators,¹⁷ in reactions following the intravenous injection of proteose or of typhoid vaccine measured the rapid production of heat during chill and remarked on the original lack of uniformity of its distribution—so that rectal temperatures could not be relied on as an accurate reflection of body temperature. They also commented on drops in cutaneous temperature, but Du Bois found many variations, even to the point where cutaneous temperatures were higher than rectal temperatures.¹⁸ Although muscle temperatures were found by some to drop,¹⁶ Nedzel could observe no change in studying thigh temperatures of dogs during bacterial chill.¹⁹

My findings were in agreement with these previous results. Rectal temperatures, recorded by an automatic device or read at frequent intervals with an ordinary thermometer, showed in 10 cases a steady rise during chill, in 4 of these preceded by a fall of from 0.4 to 1.0 F. Of these 10, chills in 2 were due to pyelitis and in the remainder had been induced by injection of typhoid vaccine. Incidental readings in 6 other cases of chill due to disease showed the same tendencies. In all cases the rise, if not preceded by an initial drop in rectal temperature, began only after the chill was in progress. The occasional antecedent fall might actually precede the first objective sign of tremor by several minutes or take place with its incipency.

16. (a) Petersen, W. F., and Müller, E. F.: The Splanchnoperipheral Balance During Chill and Fever, *Arch. Int. Med.* **40**:575 (Nov.) 1927. (b) Müller, E. F., and Petersen, W. F.: Ueber das Verhalten der Skelettmuskulatur im Schüttelfrost, *München. med. Wchnschr.* **74**:1218 (July 22); 1276 (July 29) 1927.

17. Barr, D. P.; Cecil, R. L., and Du Bois, E. F.: Temperature Regulation After the Intravenous Injection of Proteose and Typhoid Vaccine, *Arch. Int. Med.* **29**:608 (May) 1922.

18. Du Bois, E. F.: The Mechanism of Heat Loss and Temperature Regulation, *Stanford Univ. Pub. Univ. Series, M. Sc.* **3**:387, 1937; Heat Loss from the Human Body, *Bull. New York Acad. Med.* **15**:143 (March) 1939.

19. Nedzel, A. J.: A Study of Muscle Temperature During Bacterial Chill, *Proc. Soc. Exper. Biol. & Med.* **32**:279 (Nov.) 1934.

Cutaneous temperatures, recorded by a thermocouple with multiple leads in 6 patients receiving typhoid vaccine, were more variable. By having the patient lie for some time practically uncovered in a room heated to 70 F., it was possible to induce mild chills with small doses without any change in cutaneous temperature. More severe chills or reactions brought on in a cooled room revealed consistent drops in cutaneous temperature, the fall beginning with the onset of tremor or barely preceding it. In 2 patients, each with a sympathectomized extremity, no change took place on the affected limb as compared with a definite drop on the intact side. As the chill progressed cutaneous temperatures rose above normal in those patients whose febrile response was most marked, while in those who reacted mildly temperatures remained unchanged throughout.

Heart Rate.—Similar to the observations of Barcroft and Marshall²⁰ and of Swift¹³ on chills following exposure to cold was the finding that there is nearly always a slowing of the pulse rate during the chill of disease. A drop of from 4 to 16 beats per minute was found in 8 of 10 patients at the start of tremor, while in 2 it remained unchanged. In all cases, however, a progressive rise in heart rate appeared while the chill was in operation or concomitantly with the fading of the chill and the accompanying rise in temperature. The role of fear and apprehension on the part of the patient must be evaluated in the interpretation of these findings.

Respiration.—But little change occurs in the respiratory rate. In 6 of the 10 more adequately studied patients it showed a slight decrease; in 2 it remained unchanged, and in 2 there was a slight increase. Swift noted a minor slowing of rate in the majority of his cases.¹³ On the other hand, other changes took place in the character of the respiratory movements. In general, breathing during chills was shallower and jerky, at times with long sighs interspersed among shorter movements, at times even with short periods of apnea. Often it appeared that respirations shifted from a thoracic to an abdominal type. During chill, mouth breathing through pursed, partially closed lips was common—even to the point where an audible hissing breathing sound could be readily heard.

Blood Pressure.—Scully²¹ attempted to follow the changes in blood pressure during chills induced by intravenous injection of foreign proteins. He observed a questionable rise but felt that accurate measurements were difficult to obtain. By taking repeated readings before, during

20. Barcroft, J., and Marshall, E. K., Jr.: Note on the Effect of External Temperature on the Circulation in Man, *J. Physiol.* **58**:145 (Dec.) 1923.

21. Scully, F. J.: The Reaction After Intravenous Injections of Foreign Proteins, *J. A. M. A.* **69**:20 (July 7) 1917.

and after induced malarial chills in 4 patients and chills in 4 others who had received typhoid therapy, a slight but consistent rise was observed, and incidental readings on 8 other patients with chills of disease were more elevated than those made after the chills had subsided.

Posture.—The desire to avoid motion of any kind was invariably seen in every case of chill that was observed. The patient, probably to avoid the increased sensation of cold produced by movements of air, often assumed a double-up position on his side—knees drawn up, arms flexed across the chest or held tightly to the sides, neck usually drawn forward or flexed and head often buried under the blankets. Pull the covers suddenly from a patient with a severe rigor and he may adopt the position described.

Skin.—Maragliano²² observed that with rising body temperature peripheral vasoconstriction takes place. Numerous investigators have described the changes that accompany the chill of disease or lowered external temperature.²³ My findings are merely corroboratory.

The skin is pale, occasionally with a peripheral cyanotic tinge (Cowie and Calhoun²⁴ found no methemoglobin). Usually the skin is dry, but a transient expression of sweat may sometimes be noted near the onset of a chill. Goose flesh may be apparent, together with erection of hairs, and is more often limited to exposed parts. The skin usually feels cool to the touch, but may actually feel warmer than normal—this is the rule after the reaction has passed its climax. The often mentioned peripheral constriction was confirmed in 2 cases by microscopic examination of the vessels of the nail beds.

Muscle Tremor.—Richet¹ found that the rate of tremor in dogs exposed to cold was about 10 to 12 per second. Petersen and Müller¹⁶ noted that the muscle reaction was independent of volition, that it was associated with much less fatigue than one would expect and that during chill there was loss of muscle strength.

The tremor in the chill of disease is usually rhythmic and symmetric and appears to be most marked in the extremities and the muscles of mastication. An inspiratory irregularity is also frequently seen, and in 1 case jerky diaphragmatic movements on fluoroscopic examination were seen. The accentuation of tremor during inspiration has already been mentioned. Shivering may be generalized or limited, in which case

22. Maragliano, E.: Les phénomènes vasculaires de la fièvre, Arch. ital. de biol. **11**:195, 1889.

23. Embden, G.; Lüthje, H., and Liefmann, E.: Ueber den Einfluss der Aussen-temperatur auf den Blutzuckergehalt, Beitr. z. chem. Physiol. u. Path. **10**:265, 1907. Müller.⁵ Footnote 16. Du Bois.¹⁸

24. Cowie, D. M., and Calhoun, H.: Nonspecific Therapy in Arthritis and Infections, Arch. Int. Med. **23**:69 (Jan.) 1919.

the extremities seem to have the lowest threshold. When severe, the teeth may chatter loudly, the bed in which the patient lies palpably shake and the thorax and abdominal musculature be involved. Fibrillatory tremor of individual fibers was not seen; there seems, instead, to be involvement of larger muscle groups in synchronous fashion. Increased muscle tonus is evident.

As one examines the tremor more closely, many more variations and details become apparent, and these may be confirmed by myograms (chart 3). The rapidity of muscle contractions changes constantly and in different sites; the degree and speed of contractions are rarely identical in different areas, even in homologous parts of the body; at times

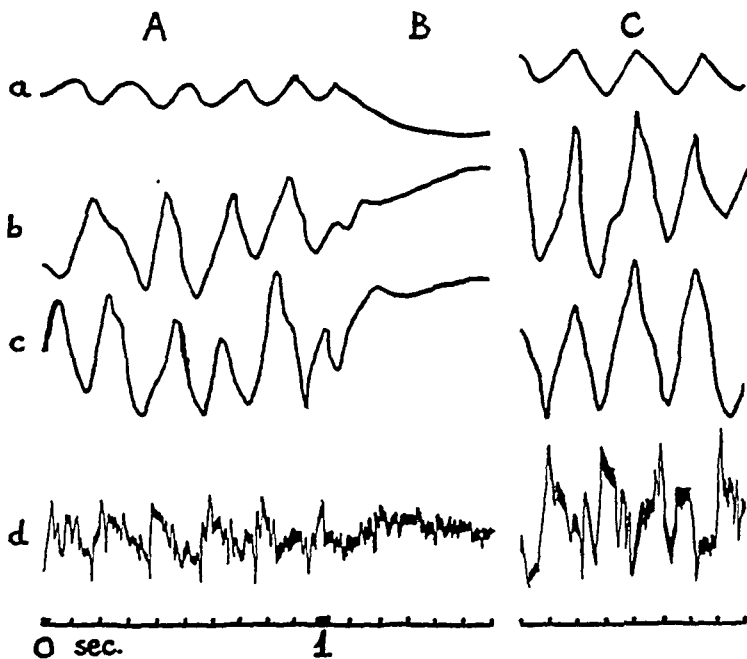


Chart 3.—Simultaneous myograms of jaw (*a*), right biceps (*b*) and left biceps (*c*) and electromyogram of left biceps (*d*). *A* shows lack of synchronous movements during chill; *B*, effect of voluntary inhibition, and *C*, occurrence of all contractions at identical times during an episode of violent shuddering.

there are a few seconds of generalized shuddering during which all motions are synchronous, and at other moments all tremors disappear completely. In the majority of cases the reaction begins with a few isolated, spasmodic movements, which then progress to a more rhythmic and uniform process. The tremor may continue without interruption or undergo any or all of the variations mentioned. The entire procedure may slowly abate, may suddenly fade or may be intermittent.

The rate of tremor in 10 patients was found to vary from 4 to 7 contractions per second, and in general it was noted that smaller muscle groups or muscles of smallest size and shortest length contracted more rapidly than did larger ones. Although the patient with a pronounced

chill cannot stop the process by volition completely, he can usually decrease its severity for short periods. A mild tremor may be completely abolished. Voluntary restraint was achieved, it was observed, by gripping the sides of the bed or by bracing the body, often by taking a deep breath and holding it and tensing the entire body musculature. When asked to try to stop shaking, the patient usually responded with such maneuvers.

By comparing a voluntary tremor with that of a patient during chill, it was easy to confirm the observation of Petersen and Müller regarding fatigue—a few minutes will produce marked tiredness if the tremor is not involuntary, while a genuine chill may go for hours without recognition of effort. And, lastly, 1 patient showed a 40 per cent reduction in hand muscle strength as measured with a dynamometer.

Other Signs.—In general the pupils appear to be slightly dilated, the deep tendon reflexes diminished and the skin hypersensitive to touch and pinprick while a chill is in progress.

LABORATORY FINDINGS

Blood Count.—Jobling, Petersen and Eggstein²⁵ described an initial leukopenia occurring after injection of trypsin, followed later by leukocytosis. Scully,²¹ giving foreign proteins intravenously, reported an average leukocyte count of 14,000 at the time of injection, 5,000 during chill and a rise to 40,000 about eight hours after the material had been introduced. Cowie and Calhoun²⁴ confirmed the lowering of the leukocyte count after intravenous injection of typhoid protein and stated that the change was associated with, but was not necessarily proportional to, the dose. Also mentioned by them were the appearance of myelocytes, nucleated red cells, often atypical cells, particularly of the lymphocyte series, and a questionable increase in platelets. Müller and Petersen²⁶ noted a drop in the number of leukocytes, but gave no specific details, and stated that blood from visceral vessels showed a leukocytosis at the same time.

Complete blood counts were done for 5 patients ten minutes before and ten minutes after the onset of an induced typhoid chill and before and after three malarial chills in 2 other patients. In every case hemoglobin determinations (Sahli) and red cell counts remained within the limits of technical error.

25. Jobling, J. W.; Petersen, W., and Eggstein, A. A.: Serum Ferments and Antiferments: Studies on Ferment Action, *J. Exper. Med.* **22**:141, 1915.

26. (a) Müller, E. F., and Petersen, W. F.: Ueber das splanchno-periphere Gleichgewicht der Gefässpermeabilität und seine klinische Bedeutung, *Klin. Wchnschr.* **5**:53 (Jan. 8) 1926; (b) Die Bedeutung der physiologischen Schwankungen in den peripheren Leukocytenzahlen, *ibid.* **5**:136 (Jan. 22) 1926; (c) footnote 16*b*. (d) Petersen and Müller.^{16a}

The leukocyte count, on the other hand, showed a consistent drop, from an average of 9,000 to one of 4,000 (there was a drop of more than 2,500 in every instance). Counts were practically identical whether the blood was obtained from the antecubital vein, the finger tip or the ear, but when in 1 patient an arm was immersed in hot water for five minutes during a chill, the finger tip count on that side was similar to the prechill count made on the same finger, while on the unheated side there were 4,600 fewer leukocytes per cubic millimeter. The same failure to observe a drop in the number of leukocytes during chill was seen in another 2 patients when blood was taken from the brachial artery and compared with a sample from a vein on the same side which demonstrated the usual fall.

On differential smears a slight "shift to the left" as measured by the Arneth index was found in all 5 patients. No myelocytes or nucleated red cells were seen, and platelet counts done on 2 patients were within the variation of normal error.

Chemical Constituents of the Blood.—Studies of the blood sugar as influenced by low environmental temperatures have resulted in conflicting reports. Several observers stated that the dextrose content of the blood varies inversely with the external temperature and others that the blood sugar falls after exposure to cold,²⁷ while Swift¹³ found the levels unchanged. In 5 cases of typhoid or malarial chill, we were unable to observe any consistent or significant change in the sugar content of samples of blood taken after the chill as compared with that of samples taken fifteen minutes before the onset of chill.

Jobling, Petersen and Eggstein²⁵ reported an immediate rise in serum protease and esterase, together with lengthening of the coagulation time and a drop in antiferments during chills brought on by injection of trypsin. They found no change in the nonprotein nitrogen content of the blood. In 2 cases of typhoid-induced chill no alteration in either nonprotein nitrogen or total protein was observed.

Hematocrit Readings.—The ratio of cells to serum showed a slight increase in three of five determinations performed on samples of blood taken during induced chills as compared with those on samples taken before the onset of chill. No change was found in 2 cases, in which the tremors were mild and of short duration, whereas in the remaining cases, in which the tremors were of much greater severity, the hematocrit readings were higher.

Urine.—Specimens of urine obtained before and during chill of disease (3 cases) and after injection of typhoid vaccine (3 cases)

27. Freund, H., and Marchand, F.: Ueber Blutzucker und Wärmeregulation, Arch. f. exper. Path. u. Pharmacol. **73**:276 (Sept.) 1913. Embden, Lüthje and Liefmann.²³

showed no changes in sediment, nor was albumin or sugar detectable. The decrease in specific gravity, however, which occurred in all instances, ranged from 0.003 to 0.008.

Other Observations.—According to Petersen and Müller,²⁸ an observation on a single patient showed cessation of stomach contractions during chill produced by intramuscular injection of sterile milk, and these workers claimed that chill is accompanied by gastric dilatation and sometimes by vomiting, increased volume and acidity of gastric juice, increased metabolic activity of the viscera, leukocytosis in the internal vessels (as opposed to a drop in the number of leukocytes in the peripheral vessels), increased lymph production and a higher protein content of the lymph.

Barcroft and Marshall²⁹ reported an increase in the minute volume output of the heart with exposure to cold. With the knowledge that nonspecific positive Wassermann reactions occur in patients with fever, Besancon and Mayer²⁹ performed 200 Kolmer and Kahn tests on 33 patients with syphilis receiving chills from protein therapy. They found that 26 per cent gave reactions different from those in control tests, some tending toward increasing positivity and others toward negativity.

ROLE IN TEMPERATURE REGULATION

It seemed obvious to early observers that a chill was accompanied by increased energy requirements and, therefore, by increased heat production, and that the cold skin of the shivering patient probably resulted in decreased elimination of heat from the body—the net result being a rise in temperature. Arguments took place, however, as to which mechanism played the more important role.

In 1871 von Liebermeister³⁰ noted the rise in carbon dioxide production during malarial chills, and eleven years later Fredericq's long discussion of temperature regulation appeared.³ At the start of this century calorimetric observations on a patient with malaria caused Likhatscheff and Avroroff³¹ to conclude that fever was due to an increase in heat production without a corresponding rise in heat elimina-

28. Petersen and Müller (footnotes 11 and 16 a). Müller and Petersen (footnotes 26 a and 16 b).

29. Besancon, J. H., and Mayer, V. R.: A Note on the Sensitivity of the Kolmer and Kahn Tests During Chill and Fever, *J. Lab. & Clin. Med.* **15**:25 (Oct.) 1929.

30. von Liebermeister, C.: Ueber die Kohlensäureproduktion im Fieber und ihr Verhältniss zur Wärmeproduction, *Deutsches Arch. f. klin. Med.* **8**:153 (Jan.) 1871.

31. Likhatscheff and Avroroff: Investigations of Gaseous and Heat Exchange in Fevers, *Rep. Imp. Mil. Acad., Russia* **5**:239, 1902.

tion. This ratio between generation and loss in producing changes in body temperature was also stressed by Sjöström.³² Ott,³³ using direct calorimetric methods, also on a patient with malaria, expressed the opinion that both a rise in production and a decrease in elimination took place, while Barr and Du Bois,³⁴ in 1918, found a threefold increase in heat production as measured by oxygen consumption but observed no significant change in elimination.

Later Barr, Cecil and Du Bois¹⁷ found no essential difference in thermogenesis whether the chill was produced by malaria or by the injection of proteose or typhoid vaccine. In either case the respiratory quotient would rise, the body would rapidly create more heat without altering in its ability to lose it. Delcourt-Bernard³⁵ claimed that the tremor per se raised the heat production about 20 per cent., as compared with a variable but greater percentage of rise during fever.

The work of Du Bois and his associates completed the present concept of the role of chill in temperature regulation. I have nothing further to add to their recent and brilliant contributions. Du Bois¹⁸ was the first to point out that heat loss from the body involved radiation, vaporization and convection (practically none is lost by conduction) and that the net change in elimination depended on the sum of changes in each of these components. Thus, during chills, heat loss by radiation falls because of vasoconstriction, but tremor might result in an even greater increase in loss through added convection. A cold skin may under the conditions of chill give off more heat than a hot one, a fact not previously appreciated. Hardy, Milhorat and Du Bois⁴ noted that on exposure to cold a slight rise in the metabolic rate accompanies the involuntary tenseness of muscles just prior to a chill and that it increases to two or three times normal during chill, with an increase in heat loss of only 10 to 15 per cent.

In summary, a chill is associated with a marked increase in metabolic needs and a resultant rapid rise in heat production. This is due in part to the energy produced by the muscle tremor and, as Petersen and Müller suggested,¹⁶ perhaps to increased visceral metabolic activity as well. Changes in heat elimination during chill are comparatively slight,

32. Sjöström, L.: Ueber den Einfluss der Temperatur der umgebenden Luft auf die Kohlensäureabgabe beim Menschen, *Skandinav. Arch. f. Physiol.* **30**:1, 1913.

33. Ott, I.: *Fever: Its Thermotaxes and Metabolism*, New York, Paul B. Hoeber, 1914.

34. Barr, D. P., and Du Bois, E. F.: The Metabolism in Malarial Fever, *Arch. Int. Med.* **21**:627 (May) 1918.

35. Delcourt-Bernard, E.: Frisson fébrile et température périphérique, *Compt. rend. Soc. de biol.* **112**:724 (Jan.) 1933; L'accès fébrile chez l'homme, *ibid.* **113**: 412 (April) 1933.

and heat loss may even increase to a small extent. The result of increased production, in the absence of a comparable change in elimination, is a rise in body temperature.

MECHANISM OF CHILLS

Literature.—Nearly all of the studies done on this subject deal with experimental chills produced by lowered environmental temperature. Nevertheless, because of the close similarity between such chills and the chill of disease, it becomes obligatory to include them in this review.

1. In 1874 Goltz³⁶ demonstrated that exposure to cold of a dog's hind extremities after section of the cord resulted in shivering of the upper part of the body but none below the operative site. He suggested a medullary center as being responsible. A few years later Fredericq³ raised the question of a possible reflex mechanism influenced by the cooling of the blood stream, although he favored a cutaneous reflex with the medulla as headquarters for the shivering response. Richet,¹ in 1892, stated that chills could be induced by cooling and by disease and also noted no shivering in dogs below the level of transection of the cord.

Sherrington and Laslett³⁷ mentioned that dogs with section of the thoracic portion of the cord shivered only cephalad to the lesion, and in 1924 Sherrington³⁸ concluded that shivering (after immersion of dogs in ice water) was not a spinal reflex, as cutting the afferent root fibers on one side still resulted in tremor synchronous with, though somewhat less than, that on the unaffected side. He therefore expressed the opinion that shivering must be due either to a cutaneous stimulus or to direct cooling of a central thermotaxic mechanism. More recently, Hermann and Morin³⁹ also reported no shivering in the spinal animal.

In 1935 Uprus, Gaylor and Carmichael⁴⁰ produced shivering in patients with neurologic diseases by immersion of the legs in cold water. Two patients with transverse lesions of the spinal cord and 1 with a bilateral section of the spinothalamic tract showed no shivering below the level of injury, the latter observation suggesting to the authors

36. Goltz, F.: Ueber die Functionen des Lendenmarks des Hundes, Arch. f. d. ges. Physiol. 8:461, 1874.

37. Sherrington, C. S., and Laslett, E. E.: Observations on Some Spinal Reflexes and the Interconnection of Spinal Segments, J. Physiol. 29:58 (Feb.) 1903.

38. Sherrington, C. S.: Notes on Temperature After Spinal Transection, with Some Observations on Shivering, J. Physiol. 58:405 (May) 1924.

39. Hermann, H., and Morin, G.: Sur l'origine bulbaire du frisson thermique central, Arch. internat. de physiol. 38:389 (June) 1934.

40. Uprus, V.; Gaylor, G. B., and Carmichael, E. A.: Shivering: A Clinical Study with Especial References to the Afferent and Efferent Pathways, Brain 58:220 (June) 1935.

that the efferent pathway of exposure chills might be the extrapyramidal system, lying close to the spinothalamic tract, rather than the pyramidal system. Five patients with cerebral motor lesions shivered normally on one side but had choreiform movements on the side of the damage.

2. The first attempt to localize a shivering center was reported by Bazett and Penfield⁷ in 1922. They found that cats did not shiver at low body temperatures if the brain was removed above the level of the superior colliculi. Providing the ability to regulate temperature was preserved, bilateral shivering was seen even after unilateral decerebration. They placed the responsible center as being somewhere between a section through the middle or superior colliculi and the anterior portion of the pons, on the one hand, and the upper limit of the thalamus, on the other. Rogers and Lackey⁴¹ stopped shivering in pigeons with destruction of the optic and the thalamic areas.

In 1930 Dworkin² claimed that shivering occurred in acute medullary rabbits and suggested that the center was in the lower part of the medulla or the cord. He also observed that a good spinal reflex was needed for active rigor. The recovery of heat regulation ability after destruction of the midbrain was also described by Thauer and Peters⁴² in 1937 in rabbits. Keller and Hare,⁴³ in 1932, observed that the capacity to shiver on exposure to cold was preserved in the cat with division of the brain stem at a medullary level, while removal of the hypothalamus caused loss of heat control and no shivering was seen with section at the collicular level.

On the other hand, Bazett,⁶ the same year, found that the medulla played no part, as cats decerebrated from the hypothalamus upward did not shiver. He reached the same conclusions in studies published with Alpers and Erb.⁴⁴ That monkeys failed to shiver after thalamic operations was incidentally mentioned by Ranson^{8b} in 1936. Together with Clark and Magoun,^{8a} he recently reported that no shivering was noted in cats with most of the hypothalamus destroyed and that lesions in the posterolateral portion of the hypothalamus were most apt to abolish shivering, particularly when associated with bilateral injury. Furthermore, they observed no obvious disturbance of temperature-regulating ability after damage to the thalamus. By producing highly localized

41. Rogers, F. T., and Lackey, R. W.: The Respiratory Exchange and Heat Production After Destruction of the Body Temperature-Regulating Centers of the Thalamus, *Am. J. Physiol.* **66**:453 (Nov.) 1923.

42. Thauer, R., and Peters, G.: Wärmeregulation ohne Hypothalamus, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **49**:188, 1937.

43. Keller, A. D., and Hare, W. K.: Heat Regulation in Medullary and Mid-brain Preparations, *Proc. Soc. Exper. Biol. & Med.* **29**:1067 (June) 1932.

44. Bazett, H. C.; Alpers, B. J., and Erb, W. H.: The Hypothalamus and Temperature Control, *Arch. Neurol. & Psychiat.* **30**:728 (Oct.) 1933.

damage, checked by pathologic examination, Ranson ⁴⁵ demonstrated that chills on exposure were usually prevented in cats by lesions involving the middle and posterior (tuberal and mamillary) parts of the hypothalamus.

3. The role of asphyxia and sedation was first noted in 1893 by Richet,^{1b} who found that interference with breathing or the administration of chloral hydrate to dogs would abolish the chill of exposure or make it appear only after a greater cold stimulus had been applied. Dworkin ² more recently observed that anesthetics depress the chill of low environmental temperature in proportion to the dose. In 1936 Tournade ⁴⁶ showed that this was not effected through the carotid sinus and that injected asphyxic blood had no intrinsic power to check a dog's tremor. He concluded that the mechanism was central. Later, Tournade, Raynaud and Chardon ⁴⁷ demonstrated that rapid exsanguination arrested shivering. In chills following serum administration, as well as malarial chills and chills induced by injections of typhoid vaccine, Beeson and Hoagland ⁴⁸ were able to alleviate the reaction in the majority of cases by the intravenous use of a 10 per cent aqueous solution of calcium chloride, although its action was inhibited if epinephrine was used beforehand. Regardless of whether the chemical had an effect, the rise in temperature remained the same, and one of the authors has told me that calcium appeared to have no prophylactic value in preventing the chill.

4. Peripheral vasoconstriction, pallor, pilomotor stimulation and the association of tremor with rage reactions all suggested that the sympathetic division of the autonomic nervous system plays a part in chills. In 1923 Hartman, McCordock and Loder ⁴⁹ claimed that exposure to cold resulted in increased epinephrine secretion, as dilatation of the denervated iris occurred providing the adrenal glands were not removed or denervated. Müller and Petersen repeatedly emphasized a splanchno-peripheral autonomic balance in the chill of disease.⁵⁰ They asserted that the outward manifestations of chill are proof of peripheral sym-

45. Ranson, S. W.: The Hypothalamus, Dunham Lecture, Harvard Medical School, 1940.

46. Tournade, A.: La sédation du frisson thermique par l'asphyxie, *Compt. rend. Soc. de biol.* **121**:1525 (Feb.) 1936.

47. Tournade, A.; Raynaud, R., and Chardon, G.: Acétylcholine et frisson thermique, *Compt. rend. Soc. de biol.* **130**:1307, 1939.

48. Beeson, P. B., and Hoagland, C. L.: Use of Calcium Chloride in Relief of Chills Following Serum Administration, *Proc. Soc. Exper. Biol. & Med.* **38**:160 (Feb.) 1938; The Use of Calcium Chloride in the Treatment of Chills, *New York State J. Med.* **40**:803 (May 15) 1940.

49. Hartman, F. A.; McCordock, H. A., and Loder, M. M.: Conditions Determining Adrenal Secretion, *Am. J. Physiol.* **64**:1 (May) 1923.

50. Müller.⁵ Petersen and Müller.¹¹ Footnote 26.

pathetic stimulation, and splanchnic dilatation, together with decreased gastric contractions and increased visceral metabolic activity, is evidence of internal parasympathetic stimulation.

Cannon and associates,⁵¹ using a desympathectomized heart preparation, found that cats fed cold fluids through a stomach tube had a rise in epinephrine in the blood even before shivering and that tremor occurred sooner if the adrenal glands were denervated. Britton⁵² rendered cats hypoglycemic with insulin and found that shivering took place, together with a rise in blood sugar, on immersion in cold water if the adrenal glands were not removed. The same held true if adrenalectomy was performed and epinephrine injected. Petersen and Levinson⁵³ discovered in 1930 that epinephrine base in oil produced smaller wheals and flares in patients having malarial chills than in controls, which suggested a greater sympathetic peripheral tonus. In 1939 Tournade and his associates⁴⁷ were able to suppress exposure chills in dogs by intravenous administration of acetylcholine, again independently of changes in blood pressure or carotid innervation. Ranson⁴⁵ found that stimulation of the middle or the posterior hypothalamic region caused a rise in the blood pressure and the respiratory rate, and he postulated a sympathetic center in the same area that controlled the shivering mechanism.

Clinical Experiments.—1. By means of intravenous administration of typhoid vaccine chills were induced in 2 patients, each with a single sympathectomized leg as a result of an operative procedure performed several months before because of thromboangiitis obliterans. Shivering took place bilaterally, and there was no discernible difference in the character of tremor in either leg. Cutaneous temperatures dropped on the normal leg and remained constant on the leg in which sympathetic denervation had been achieved.

In 3 patients with flaccid hemiplegia tested several days after a cerebral accident and in 2 whose paralysis had become spastic after a longer interval, the induction of typhoid chills produced bilateral tremor, but the shivering was less marked on the affected side. When the limbs were initially flaccid, spasticity with flexion of the stronger muscle groups took place during the course of the reaction, with a return of

51. Cannon, W. B.; Querido, A.; Britton, S. W., and Bright, E. M.: The Role of Adrenal Secretion in the Chemical Control of Body Temperature, *Am. J. Physiol.* **79**:466 (Jan.) 1927.

52. Britton, S. W.: Adrenin Secretion on Exposure to Cold, Together with a Possible Explanation of Hibernation, *Am. J. Physiol.* **84**:119 (Feb.) 1928.

53. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Man and of Clinical Patients: VIII. The Intracutaneous Reactions to Injections of Pharmacologic Substances During Chill and Fever, *Arch. Path.* **9**:393 (Jan., pt. 1) 1930.

complete relaxation at the conclusion of the chill. I was able to witness a chill due to an infection of the respiratory tract in a child with complete paralysis of the legs as a result of poliomyelitis. No movements of the lower extremities were seen.

2. In an attempt to prevent chills, several of the antipyretic drugs were used prior to the time that malarial chills were expected. After a control period of 10 consecutive febrile reactions in 2 patients who had been given therapeutic tertian malaria, the use of 0.6 Gm. of aminopyrine every four hours for twenty-four hours before the next chill was due resulted in no shivering reaction and scarcely any fever. Both patients experienced a slight sense of malaise, and their temperatures rose to 100 and 100.6 F., respectively, but no tremor or sensation of cold appeared. Chills, with elevations of temperature to 104 and 105 F., occurred in both patients between twenty-six and thirty-four hours after the use of the drug had been discontinued. Blood smears, taken before, during and after the use of aminopyrine, showed approximately the same number of malarial parasites per thousand blood cells.

Aminopyrine was also found to prevent chills in patients who had taken the drug for twenty-four hours before being given typhoid vaccine intravenously. In 4 instances, in patients whose ability to react to typhoid vaccine was determined either beforehand or afterward, shivering was prevented, although the same aura and slight fever took place after the usual latent period following the injection.

These experiments were repeated with salicylates, but the results suggested that they possessed comparatively little ability as a prophylactic measure against chill. Febrile rises appeared less marked in 2 patients with malaria and in 2 being given typhoid vaccine therapy, but the variability of repeated reactions in the same patient makes this observation inconclusive. Chills occurred in all cases.

In 3 of 7 patients with pneumonia or pyelitis chill reactions following transfusion were stopped almost instantly by the intravenous use of 3 to 10 cc. of a 10 per cent solution of calcium chloride or calcium gluconate, and in 2 others the tremor diminished markedly but did not completely disappear. This confirmed the results of Beeson and Hoagland.⁴⁸

The effects of sedation were studied by induction of typhoid chills after the administration of 0.3 Gm. of pentobarbital sodium, 0.15 Gm. of phenobarbital or 1.5 Gm. of chloral hydrate to each of 3 patients. This was controlled by use of the same dose of vaccine without sedation on the following day. Mild chills occurred in all cases, but the control test produced much more severe shivering in all 3 situations. No significant difference in the febrile response was noted, despite the difference in the degree of tremor.

On numerous occasions, in keeping with the work on asphyxia, it was found that prolonged holding of the breath made a chill more readily controllable voluntarily. In 1 case a chill was halted by having the patient breathe carbon dioxide until dyspnea had appeared.

SUMMARY AND CONCLUSIONS

Chills of disease may occur at any period of life, with the possible exception of early childhood. A latent period between the introduction of a causative agent and the onset of tremor is the rule, intravenous administration of such an agent being invariably followed by close to an hour before a reaction takes place. Many patients note an antecedent aura, and toward the end of a reaction a sense of unusual well-being may be present. The patient is often seen in an immobile, doubled-up position, with pale, cool skin, sometimes with goose flesh, constriction of superficial vessels and, occasionally, with peripheral cyanosis. A chill is usually accompanied by a steady rise in rectal temperature, which at times is preceded by an initial drop. The reaction of cutaneous temperature is not consistent; it most commonly falls but may remain unchanged. As a rule the heart rate slows, the respiratory rate becomes more irregular and the blood pressure rises.

The muscle tremor of the typical chill is rhythmic, but contractions may vary in degree and speed in different areas. The muscles display increased tonus, and the rate of tremor varies from 4 to 7 per second. Some degree of voluntary control can be achieved, particularly in the milder chills. During tremor strength is diminished, and the reaction is accompanied by surprising freedom from muscular fatigue.

A consistent drop in the white cell count occurs during chill, but it is due to a peripheral mechanism rather than to an actual decrease in the number of circulating leukocytes. Thus, a white cell count should not be done during chill, as the discovery of a leukopenia might lead to false opinions regarding therapy or prognosis. The chemical studies of the blood have revealed no significant changes during chill. The hematocrit reading may rise with severe reactions, and the specific gravity of the urine usually falls.

The purpose of chill in disease is obscure, but its role in temperature regulation is important. A chill is associated with a marked increase in metabolism and thereby a rapid rise in heat production. Changes in heat elimination during chill are comparatively slight—there may even be increased heat loss. The net result of these alterations is a rise in body temperature.

Chill represents a complex physiologic process. There is considerable evidence that a center exists in the posterior region of the hypothalamus stimulation of which causes a muscle tremor and certain peripheral

phenomena simulating increased sympathetic activity. The afferent pathway in disease reactions is obviously different from that involved in response to exposure to cold, in which a direct cooling of the blood is the probable cause of the central stimulation. The characteristic latent period and the variety of the toxic agents which can produce a chill suggest that a common denominator, perhaps of chemical nature, is the stimulating factor.

The ability of sympathectomized limbs to participate in rigor, the presence of bilateral tremor in patients with hemiplegia, the disappearance of the shivering response with disease of the anterior horn or in areas below a section of the cord—all favor an efferent pathway involving the spinal cord but probably separate from the pyramidal tract. The sympathetic-like phases of chill, the most probable cause of the subjective components, appear to be mediated by the sympathetic nerves in that their section prevents the vasoconstrictive phenomena.

Asphyxia and sedation were found to inhibit the chill of disease, thus serving to illustrate the apparent sensitivity of the shivering center and its inability to respond to stimulation if depressed by drugs or lack of oxygen. The intravenous injection of calcium chloride was confirmed as a measure producing prompt cessation of tremor in the majority of instances if instituted during chill, while aminopyrine was discovered to be highly effective in preventing chill. The dramatic action of the latter drug points toward a direct suppression of the shivering center as one of its functions.

Dr. Soma Weiss made many constructive suggestions in this study.

STUDIES ON "ESSENTIAL" HYPERTENSION

II. THE ASSOCIATION OF HYPERTENSION WITH ORGANIC RENAL DISEASE

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The role which the kidneys play in the genesis of arterial hypertension has been the subject of discussion since the days of Richard Bright. For many years it was believed that increased arterial pressure was accompanied by disease of the kidneys. Gull and Sutton¹ were the first, however, to suggest that high arterial pressure might be attributed to "arterio-capillary fibrosis." The present conception of "essential" hypertension, a condition in which the blood pressure is elevated without failure of the kidneys, is an outgrowth of the contributions of Allbutt,² Janeway³ and Volhard and Fahr.⁴ The term "essential" hypertension continues to connote a condition characterized by the *absence* of diseases to which elevated arterial pressure is considered secondary and as such is of inexact meaning. Since the work of Goldblatt⁵ in producing experimental hypertension by interference with the renal blood supply, the importance of the kidneys in hypertension has again been emphasized, and cases of a condition in human beings analogous to this variety have been reported.⁶

From the Hospital of the Rockefeller Institute for Medical Research.

1. Gull, W. W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called "Chronic Bright's Disease with Contracted Kidney," *Med.-Chir. Tr.*, London **55**:273, 1872.

2. Allbutt, C.: *Senile Plethora, or High Arterial Pressure in Elderly Persons*, Tr. Hunterian Soc., 1895-1896, pp. 38-57.

3. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, *Arch. Int. Med.* **12**:755 (Dec.) 1913.

4. Volhard, F., and Fahr, T.: *Die Brightsche Nierenkrankheit; Klinik, Pathologie und Atlas*, Berlin, Julius Springer, 1914.

5. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia, in *Harvey Lectures, 1937-1938*, Baltimore, Williams & Wilkins Company, 1939, vol. 33, p. 237.

6. Leiter, L.: Unusual Hypertensive Renal Disease: Occlusion of Renal Arteries (Goldblatt Hypertension); Anomalies of Urinary Tract, *J. A. M. A.* **111**:507 (Aug. 6) 1938.

The identity of all cases of "essential" hypertension has been seriously called into question, and a classification of them has been attempted.⁷ By definition, this condition is one in which the arterial pressure is elevated without the presence of organic renal disease. The extent, however, to which investigation of the kidneys for organic disease has been extended is not stated, and it is usually implied that when renal function is normal in the presence of arterial hypertension and abnormal urinary constituents are not found the condition is called "essential" hypertension.

If a searching history is taken and more thorough investigation of the genitourinary tract is made, in a large number of cases there is found either a history suggesting organic renal disease prior to the development of hypertension or certain physical and urinary changes inconsistent with the clinical appearance of "essential" hypertension,⁷ although other aspects of the physical condition, the course and the eventual outcome may in all respects resemble those in other cases of what is considered as "essential" hypertension. A number of such cases have been reported. Longcope⁸ was perhaps the first to recognize that chronic bilateral pyelonephritis and arterial hypertension are associated. Pyelonephritis and hypertension have in fact been reported to occur during and after toxemia of pregnancy⁹ and in childhood,¹⁰ sometimes being accompanied by marked changes in blood vessels.¹¹ Examples of other renal diseases with hypertension have appeared in the literature, and in a few¹² blood pressure has been lowered by removal of a single affected kidney.

7. (a) Schroeder, H. A., and Steele, J. M.: Abnormalities of the Urinary Tract in "Essential Hypertension," *Proc. Soc. Exper. Biol. & Med.* **39**:107, 1938; (b) Studies on "Essential" Hypertension: I. Classification, *Arch. Int. Med.* **64**:927 (Nov.) 1939. (c) Cohn, A. E.; Schroeder, H. A., and Steele, J. M.: Essential Hypertension and Diseases of the Kidneys, *Tr. A. Am. Physicians* **54**:82, 1939.

8. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, *Ann. Int. Med.* **11**:149, 1937.

9. (a) Peters, J. P.: Nature of Toxemias of Pregnancy, *J. A. M. A.* **110**:329 (Jan. 29) 1938. (b) Peters, J. P.; Laviates, P. H., and Zimmermann, H. M.: Pyelitis in Toxemias of Pregnancy, *Am. J. Obst. & Gynec.* **32**:911, 1936. (c) Zimmermann, H. M., and Peters, J. P.: Pathology of Pregnancy Toxemias, *J. Clin. Investigation* **16**:397, 1937.

10. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, *J. Clin. Investigation* **16**:889, 1937.

11. (a) Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18**:221, 1939. (b) Guild, H. G.; Kindell, F. B., and Gibson, T. A.: Arteriosclerosis in Childhood, with Report of Two Cases, *Bull. Johns Hopkins Hosp.* **62**:159, 1938.

12. (a) Barker, N. W., and Walters, W.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Treatment by Nephrectomy, *Proc. Staff Meet., Mayo Clin.* **13**:118, 1938. (b) Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension: Preliminary Report, *J. Urol.* **39**:627,

Because of recent emphasis on the importance of the kidneys in hypertension and because many of our patients are known to have sustained some renal damage before the blood pressure became elevated, we have studied the urinary tract further in an attempt to discover other renal lesions in cases which have been believed to represent "essential" hypertension. The cases of 250 patients have been studied. Roentgenographic examination of the renal pelves and ureters after the intravenous injection of diodrast (3.5 diiodo-4-pyridone-N-acetic acid and diethanolamine), that is, by excretory urography, was undertaken in 178 cases. Cultures of the urine were made whenever there was a suggestion of the presence of infection. Cystoscopic examination was performed and studies of the functions of the two kidneys were made separately in 42 cases. Evidence of renal abnormalities antedating the onset of hypertension was carefully sought, and all renal ailments other than the condition assumed to be secondary to arterial hypertension (i. e., arteriolonephrosclerosis) were considered important.

OBSERVATIONS

Renal Calculus.—Damage to the kidneys by calculus without marked diminution of renal function may precede or be associated with hypertension. In 10 cases the patients suffered attacks of pain due to renal calculus before the onset of hypertension or were found to exhibit stone in the urinary tract at the time hypertension was well established (table 1). In 3 of these cases there was coexistent infection, and in 2 some degree of hydronephrosis with constriction of the ureter at the ureteropelvic junction existed; at autopsy aberrant arteries were found crossing the ureteropelvic junction. Attacks of renal calculus may be followed by "malignant" hypertension with diminution in function of the affected kidney even after the calculus has disappeared, as is illustrated in case 9. In 2 other instances this was the course of events. Occasionally the removal of a calculus is intimately associated with the onset of hypertension (case 1).

Pyelonephritis.—Severe renal damage, the result of chronic pyelonephritis, has been followed by hypertension with renal insufficiency.⁸ Toxemia of pregnancy resulting in chronic hypertension has been observed in association with pyelonephritis.⁹ In 8 of our cases there was a history of pyelonephritis or pyelitis before or at the time of onset of hypertension (table 2). In 5 the onset occurred with the pregnancy

1938. (c) Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, *ibid.* **39**:611, 1938. (d) Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, *J. Clin. Investigation* **16**:889, 1937. (e) Pincoffs, M. C., and Bradley, J. E.: The Association of Adenosarcoma of the Kidney (Wilms' Tumor) with Arterial Hypertension, *Tr. A. Am. Physicians* **52**:320, 1937.

TABLE 1.—Renal Calculi

Case No.	Name	Sex	Family History *	Age at Onset, †	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ¶	Urea Clearance, ¶ per Cent Normal	Present State; # Cause of Death	Comment **
					High	Low	Arterio-sclerosis	Hemor-rhage Exudate					
1 ††	P. M.	♂	0	23	6	210/140	150/100	0	+++	Calculus from 21 to 23	92	L	Calculus removed before onset; slight hydronephrosis; UPJ obstruction
2	M. H.	♂	?	31	10	210/130	180/125	+	0	Calculus at 26	62	D; ?	Not well followed
3 ††	D. W.	♂	+++++	41	6	210/140	200/130	+	+++	Calculi from 37 to 45	94	D, R	Multiple calculi in left kidney
4	J. C.	♂	0	55	5	200/120	160/110	+	0	Calculus removed at 45 and passed at 48	84	D; Ce	Pyuria; calculus remained
5	I. M.	♂	+	45	1	270/160	260/140	+	+++	Calculus from 39 to 42 (3 passed)	..	D; O	Rapid course
6	L. B.	♂	+	45	9	180/130	145/100	0	0	Calculus at 41 and 45	101	L	Calculus still present; infection
7 ††	H. S.	♂	+	34	2	220/140	180/125	0	+++	Calculus at 22 and 34	83	D; C, R	Moderate bilateral hydronephrosis, pyelonephritis; UPJ obstruction
8	H. M.	♂	..	29	10	180/110	155/90	0	0	88	L	Calculus at present
9	R. K.	♂	+	38	2	250/160	220/140	0	++	Calculi at 34 and 36 (passed)	44	D; R	Poorly functioning, contracted left kidney
10	R. F.	♂	+	34	2	200/140	180/130	0	+	Calculi at 29, removed at 34	121	D	Right hydronephrosis; death from embolism after nephrectomy

In this table and in tables 2 to 7, inclusive, and 9 and 10, the symbols used in the column heads have the following significance:

* The + signifies one relative in a preceding generation who was suffering from hypertension.

† Unless otherwise indicated, the onset of hypertension was known to have occurred within two years of the age given.

‡ The figures given indicate the average levels of blood pressure during a period of several days; single high or low readings are not noted.

§ Arteriosclerosis is indicated by tortuosity, narrowing or thickening of the arteries of the retina. "Hemorrhage and exudate" include perivascularitis, papilledema and scars.

¶ The specific gravity of the morning specimen of urine after twenty-four to thirty-six hours of a regimen of rigid restriction of fluids. The highest figure is reported.

The urea clearance was determined by the method of Van Slyke.

** L means living in June 1940; D, dead; C, cardiac failure or coronary accident; R, renal failure; Ce, apoplexy.

UPJ obstruction means angulation of the ureter at the ureteropelvic junction, as visualized in the excretory urogram. Poor excretion of diodrast is indicated by lack of visualization of the renal pelvis and ureter in repeated excretory urograms.

†† Case previously reported by Page and Heuer.¹³

‡‡ Case in which an affected kidney was removed, reported by Schroeder and Fish.¹¹

TABLE 2.—*Pyelonephritis*

Case No.	Name	Sex	Family History *	Age at Onset	Duration, † Years	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ¶	Urea Clearance, ¶ per Cent Normal	Present State; # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
11	H. F.	♀	+	24	9	260/140	220/120	0	++ + +	Renal colic from 19 to 25; pyuria during pregnancy	1.010	13	D; R	Onset associated with pyelonephritis; infection
12	M. F.	♀	0	29	8	300/160	220/130	+	+	Pyelitis from 21 to 30; toxemia of pregnancy	1.027	77	L	Diminished function of right kidney with UPJ obstruction
13	M. P.	♀	+++ +	29	16	260/170	210/150	±	++	Pyuria with toxemia of pregnancy	1.022	54	D; C, R	Marked scarring of kidneys
14	A. L.	♀	+	33	1	230/150	210/130	0	+	D; R	Multiple abscesses of kidneys; nephrosclerosis
15 ††	B. W.	♀	+	21	8	250/145	225/130	+	+	Pyuria from 9 to 21; toxemia of pregnancy at 21	1.017	72	D; R	Functionless; contracted left kidney with dilated pelvis; infection
16 ††	F. C.	♀	+	25	1	220/140	190/120	0	0	Pyuria at 6	1.025	87	L	Poorly functioning, contracted left kidney
17	L. G.	♀	0	24	7	210/120	180/110	0	0	Pyelitis of pregnancy at 18 and 24	1.017	63	L	Bilateral distortion of the pelvis with infection
18	F. C.	♀	+++ +	21	7	205/140	190/135	+	0	Pain at 21	1.017	63	L	UPJ obstruction with infection

For interpretation of symbols not defined here, see table 1.

†† Case in which an affected kidney was removed, reported by Schroeder and Fish.¹¹

in which "toxemia" developed. An example of this is given (case 12). In 2 cases the patient exhibited failure of renal function when first observed by us; hypertension was present before there was retention of nitrogen in the blood, but the function of the kidneys was not known exactly, so that there may be doubt concerning the diagnosis of "essential" hypertension. In both an aberrant renal artery constricting the ureteropelvic junction was observed at autopsy. Infection of the urine was demonstrated in 25 cases.

Hydronephrosis.—It is not well understood that hydronephrosis without renal insufficiency may be associated with hypertension closely resembling the so-called essential variety. One case of this type has been reported^{7b}. In 9 cases there was exhibited well marked hydronephrosis with hypertension (table 3), and in 35 others some degree of it was demonstrable (excretory urograms). It was also seen along with other abnormalities in 10 cases. Hydronephrosis may not always be accompanied by diminution in renal function (case 19) unless destruction of a considerable amount of a kidney is present (case 24, reported previously¹³). Such abnormalities may accompany hypertension in older as well as in younger persons (case 22).

Ptoxis.—Nephroptosis may not appear significant in association with hypertension unless there is diminution of function of the affected kidney or evidence of obstruction to the flow of urine. Nine patients exhibited this abnormality (table 4), and 7 others showed it in lesser degree in association with other lesions. That ptosis of the kidney may result in diminution of renal function is well illustrated (case 28).

Miscellaneous Renal Lesions.—Various renal abnormalities were observed in 8 cases (table 5). In 2 hypertension followed severe renal damage, apparently caused in 1 by a burn from a sun lamp (case 41) and in the other by an attack of alkalosis.¹⁴ There were also 1 case of congenital horseshoe kidney, 1 of double kidney with hydroureter; 1 of scarred and atrophic kidney with hydroureter, 1 of unilateral polycystic kidney, 1 of tuberculous destruction of one kidney and 1 in which a kidney was completely replaced by a calcified cyst (case 39).

Probable Renal Disease.—There was evidence of some renal abnormality preceding or associated with the onset of hypertension in 28 cases (table 6). In 7 persistent albuminuria preceded the onset of hypertension. No further investigation of the genitourinary tract was

13. Page, I. H., and Heuer, G. J.: Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots, Arch. Int. Med. **59**:245 (Feb.) 1937.

14. Steele, J. M.: Renal Insufficiency Developing During Prolonged Use of Alkalis: Report of a Case, J. A. M. A. **106**:2049 (June 13) 1936.

TABLE 3.—*Hydronephrosis*

Case No.	Name	Sex	Family History *	Age at Onset	Duration,† Years	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ¶	Urea Clearance, % per Cent Normal	Present State, # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
19 ††	J. G.	♂	++	21	11	230/140	190/100	0	0	Albuminuria "always"	1.023	111	D; anuria	Bilateral hydronephrosis with UPJ obstruction
20 ††	G. R.	♂	?	29	3	210/150	190/130	0	+	Renal colic at 14	1.025	79	L	Marked left hydronephrosis and hydroureter
21 ††	A. L.	♀	++	23	6	220/150	260/130	0	+	Renal colic; slight left hydronephrosis at 19	1.022	100	L	Marked left hydronephrosis, moderate right hydronephrosis; UPJ obstruction
22	E. Z.	♀	0	45	15	210/130	180/120	++	+	Albuminuria at 43	1.030	74	D; C	Left hydronephrosis; calculus on right side; scars of old hemorrhages in ocular fundi
23	F. K.	♀	+	23	3	230/170	210/160	0	+	1.028	71	L	Ptosis of right kidney with moderate hydronephrosis and UPJ obstruction
24 §§	P. S.	♀	0	24	6	220/130	160/100	0	0	Pregnancy	1.023	115	L	Bilateral hydronephrosis with UPJ obstruction
25	M. L.	♀	0	36	4	200/130	180/120	+	0	1.028	108	L	Ptosis of right kidney and hydronephrosis with infection
26	I. R.	♀	0	33	1	240/150	210/130	0	++	1.025	90	L	Bilateral UPJ obstruction with aberrant artery
27	J. T.	♀	+	18	15	240/140	210/130	+	0	1.029	90	D; Cc	Right hydronephrosis with UPJ obstruction

For interpretation of symbols not defined here, see table 1.

†† Case previously reported by Schroeder and Steele.^{7b}

‡‡ Case in which an affected kidney was removed, reported by Schroeder and Fish.⁴¹

§§ Case previously reported by Page and Heuer.¹³

TABLE 4.—*Ptosis*

Case No.	Name	Sex	Family History *	Age at Onset	Duration,† Years	Extremes of Blood Pressure †		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ‖	Urea Clearance, ‖ per Cent Normal	Present State;# Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
28 ††	M. B.	♀	+	24	9	200/130	170/100	0	0	Pain from 22 to present	1.036	119	L	Right ptosis with poor function
29	G. F.	♀	++	19	4	190/100	150/80	0	0	1.035	166	L	Bilateral ptosis; small right kidney; albumin from right kidney
30	B. B.	♂	++	51	7	190/115	150/95	++	0	1.027	98	L	Right ptosis with slight hydro-nephrosis and UPJ obstruction
31	H. M.	♂	0	39	30	160/100	150/90	+	+	Albuminuria at 39	1.025	68	D; ?	Bilateral ptosis; no excretion of diodrast by right kidney
32	K. B.	♀	++++	32	6	240/140	210/125	0	0	1.023	102	D; Co, R	Right ptosis with UPJ obstruction
33	R. M.	♀	++++	55	5	180/110	130/90	0	0	Operation for renal infection at 50	1.025	73	L	Right ptosis; moderate hydro-nephrosis with UPJ obstruction; infection
34	G. L.	♀	+	34	4	190/130	140/95	0	0	1.031	76	L	Right ptosis; slight bilateral hydronephrosis with UPJ obstruction
35	H. B.	♀	+++	36	16	200/115	170/100	+	0	1.025	75	L	Right ptosis; slight hydronephrosis with UPJ obstruction
36	N. V.	♀	++	42	10	260/110	180/100	+	0	1.033	80	L	Bilateral ptosis with UPJ obstruction

For interpretation of symbols not defined here, see table 1.

†† Case in which an affected kidney was removed, reported by Schroeder and Fish.¹¹

TABLE 5.—Miscellaneous Renal Diseases

Case No.	Name	Sex	Family History *	Age at Onset	Duration, † Years	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration	Urea Clearance, per Cent Normal	Present State; # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemorrhage and Exudate					
37	L. W.	♂	0	36	4	185/110	150/100	+	0	?	Urea index normal	D; R	Cystic left kidney
38	H. A.	♂	0	47	½	280/170	240/150	0	+++	1.018	108	D; Ce	Tuberculous left kidney
39	W. A.	♂	+	23	9	210/145	180/125	+++	+++	Albuminuria from 7 to 28	1.015	90	D; R	Slight right hydronephrosis; calcified cystic left kidney; family history of hypertension
40 ††	C. J.	♂	++	53	2	160/100	140/90	±	0	Nitrogen retention after excessive use of alkalis at 52	1.027	147	L	Renal insufficiency with recovery; calculus subsequently, with recovery
41	L. L.	♂	++	50	3	180/130	160/115	+	0	Nitrogen retention after burn at 44	1.028	102	L	Renal insufficiency with recovery; calculus subsequently, with recovery
42	C. P.	♂	+	33	8	190/130	180/110	0	0	1.027	89	L	Double left kidney with hydro-ureter
43	F. E.	♂	++	40	7	240/130	200/115	++	++	1.026	108	D; C, R, Ce	Left hydroneur with contracted, scarred kidney; pyuria and bacilluria
44	S. S.	♀	+	22	5	190/120	170/110	0	0	1.026	80	L	Horseshoe kidney with obstruction and infection

For interpretation of symbols not defined here, see table 1.

†† Case previously reported by Steele.¹⁴

TABLE 6.—*Probable Renal Disease*

Case No.	Name	Sex	Family History*	Age at Onset	Duration,† Years	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ¶	Urea Clearance, ¶ per Cent Normal	Present State, # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
45	B. R.	♂	+	50	15	230/130	190/110	+	0	Albuminuria from 48 to 50	1.016	37	D; R	
46	W. M.	♂	+	47	7	200/120	170/110	+	+	Albuminuria at 45	1.030	109	D; C	
47	R. B.	♂	0	45	5	260/140	240/115	+	++	Albuminuria and renal colic at 44	1.022	70	D; ?	
48	F. M.	♂	0	34	7	260/150	200/130	0	++++	Albuminuria from 21 to 25	1.010	12	D; R	
49	R. R.	♂	0	28	21	180/120	170/110	Albuminuria at 27	Urea index normal	D; C	
50	F. M.	♂	0	17	9	230/135	180/130	0	++	Albuminuria, pyuria and edema at 17	1.018	16	D; R	Probably Bright's disease
51	O. T.	♀	0	31	16	210/120	180/115	+	+	Albuminuria and colic at 28	1.032	88	D; C	Persistent pyuria from 34 to 40
52	J. D.	♂	+	21	10	160/90	145/85	0	0	Hematuria at 21	1.033	112	L	Sore throat at onset; normal urogram
53 ††	M. A.	♀	0	19	1	210/140	200/120	0	+	1.032	100	L	Distorted right pelvis with poor function
54	M. An.	♀	+	20	14	210/130	190/120	+	0	1.033	186	L	Angulation of right ureter with poor function
55	C. G.	♂	+	34	7	200/120	160/100	0	0	1.021	107	L	Angulation of right ureter with poor function and infection
56	J. O.	♂	+	28	1	220/145	190/135	0	0	1.021	94	L	Slight right hydronephrosis with pyuria
57	M. M.	♀	+++	30	33	210/120	160/100	+	0	1.024	83	L	Slight right hydronephrosis with pyuria, UPJ obstruction and infection
58	V. B.	♂	+	29	10	170/120	150/100	0	0	1.030	175	L	Right hydroureter with infection

59	E. S.	♀	+++	25	9	200/120	180/115	0	0	Onset associated with pregnancy	1.029	103	L	Slight right hydronephrosis with UPJ obstruction
60	C. H.	♀	0	27	9	200/140	170/130	0	++	Albuminuria associated with pregnancy at onset	1.029	96	L	Slight right hydronephrosis
61	H. K.	♂	0	25	3	220/160	200/140	0	0	Trauma to left kidney at 24	1.026	105	L	Poor excretion of diodrast from left kidney
62	C. O.	♂	0	26	2	185/135	160/110	0	0	Pyuria at onset	1.029	113	L	Persistent pyuria
63	E. F.	♂	++	25	5	200/140	170/120	0	++	Renal colic with calculus (?) at 25 and 30	1.028	107	L	Normal urogram
64	F. E.	♂	+	37	17	180/120	160/105	+	0	1.024	85	L	Distortion of calices in right kidney; calcification in cortex
65	C. C.	♀	..	50	14	170/110	150/90	++	0	Albuminuria at 50; renal disease (?)	1.023	69	L	Slight right hydronephrosis with UPJ obstruction; pyuria
66	D. D.	♀	0	19	15	240/140	210/130	+	0	1.029	115	L	Right UPJ obstruction with slight hydronephrosis
67	A. F.	♂	+	34	11	200/130	180/120	0	0	1.024	60	L	Poor excretion of diodrast from right kidney
68	E. H.	♀	0	<34	>2	220/140	200/120	+	+	1.029	105	L	Slight right hydronephrosis with UPJ obstruction
69 ††	A. R.	♀	0	23	7	230/140	180/120	0	+++	1.027	71	D; R	Bilateral ptosis with angulation of ureters
70	U. B.	♂	0	36	1	190/120	170/110	0	0	Hematuria at 35 and subsequently	1.022	68	L	? Tuberculosis of right kidney; no excretion of diodrast; pulmonary tuberculosis at 36
71	F. R.	♂	++	28	1½	170/110	155/95	0	0	Severe pyelonephritis at 22	1.032	..	D	Stricture of left ureter
72	G. W.	♀	++	27	1	180/110	160/100	0	0	Onset associated with pregnancy	1.029	110	L	Slight right hydronephrosis

For interpretation of symbols not defined here, see table 1.

†† Case in which an affected kidney was removed, reported by Schroeder and Fish.⁴¹

†† Case previously reported by Page and Heuer.¹³

made in these cases, although in 2 of them persistent pyuria was present and in 2 a history of renal colic was obtained. Evidence of obstruction to the flow of urine was found in 12 cases; in 1 of these ptosis was also present, in 3 infection and in 3 pyuria. In 1 instance microscopic hematuria was found at the onset; in 2 a distorted renal pelvis was associated with poor renal function; in 3 there was no demonstrable excretion of radiopaque material by one kidney in photograms of the pelves, though no further investigation was made; in 2 there was persistent pyuria and in 1, a history of calculus. Although the nature of the renal disease is unknown, some degree of damage in one kidney is illustrated by case 54.

Glomerulonephritis.—In many cases indistinguishable from those of “essential” hypertension, the kidneys are found at autopsy to exhibit lesions of chronic glomerulonephritis. Often arteriolar sclerosis is present as well. To the clinician, such a condition resembles “essential” hypertension; to the pathologist, chronic Bright’s disease. It is uncertain whether renal lesions of this nature are the result or the cause of hypertension. Only when a history of acute nephritis is obtained and it is known that such an episode antedated the elevation of blood pressure can there be reasonable certainty that such renal lesions are of significance in the development of hypertension.

Little difficulty is encountered in making the correct diagnosis of a lesion of this type when renal insufficiency accompanies arterial hypertension, but there is often doubt in the absence of renal insufficiency and of pathologic urinary constituents. Fishberg¹⁵ has designated the disease in such cases the “hypertensive type” of chronic glomerulonephritis. Similar instances are included because of the close resemblance to “essential” hypertension.

There were 8 cases in which the nephritic process began before hypertension occurred or in which renal lesions similar to those found in glomerulonephritis were present at autopsy. In 7 cases the patients died of renal or renal and cardiac failure (table 7). In every case hypertension was known to have been present before there was diminution of renal function, and in all it resembled “essential” hypertension when the patient was examined in this hospital; in none were pathologic urinary constituents present. One case has previously been reported.^{7b} In a similar instance (case 78) no history of nephritis was obtained before hypertension began and the course was typical of hypertension of the “essential” type, although autopsy revealed the lesions of chronic glomerulonephritis.

15. Fishberg, A. M.: *Hypertension and Nephritis*, ed. 3, Philadelphia, Lea & Febiger, 1934.

TABLE 7.—*Glomerulonephritis*

Case No.	Name	Sex	Family History *	Age at Onset	Duration, † Years	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ¶	Urea Clearance, ¶ per Cent Normal	Present State, # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
73 ††	J. C.	♂	0	27	11	260/140	190/120	0	+++	Acute nephritis at 27	1,027	101	D; R	Glomerulonephritis at autopsy
74	J. L.	♂	0	24	2	240/140	190/110	++	++	Acute nephritis at 24	1,026	119	D; C	Cessation of albuminuria after onset
75	D. O.	♀	0	21	½	250/160	210/140	0	++	Acute nephritis at 20	1,027	Phenol-sulfonph-thalein excretion normal	D; C, R	Malignant course
76	D. H.	♂	+	37	2	245/163	220/125	0	+++	Albuminuria from 22 to 37	1,025	117	D; C	Glomerulonephritis at autopsy
77 ††	E. B.	♂	+	41	2	260/190	230/120	0	+++	Albuminuria and pyuria at 36	1,023	45	D; C, R	Glomerulonephritis at autopsy
78	A. B.	♂	+	30	12	250/150	220/140	++	+++	76	D; C, R	Glomerulonephritis at autopsy
79	R. D.	♀	0	26	7	280/150	230/140	0	++	1,022	123	D; R	Glomerulonephritis at autopsy
80	H. M.	♂	+	30	2	190/130	165/120	+	+++	Acute nephritis at 10	1,020	86	D; R	Malignant course; probably Bright's disease

For interpretation of symbols not defined here, see table 1.

†† Case previously reported by Schroeder and Steele.^{7b}‡‡ Case previously reported by Page and Heuer.¹³

TABLE 8.—Summary of Anatomic Lesions in Thirteen Cases

Case No.	Name	Kidney	Source of Material	Degree of Arteriolar Sclerosis	Microscopic Appearance		Tubular Damage	Weight of Kidney, Gm.	Anatomic Diagnosis
					Glomerular Damage	Scarring of Interstitial Tissue			
7	H. S.	Right Left	Autopsy Biopsy	+ ++++	Slight Fibrosis and thickening	++ ++++	Marked dilatation Marked; purulent exudate	190 ...	Hydronephrosis; arteriolar sclerosis Chronic pyonephrosis; nephrolithiasis; hydro-nephrosis; arteriolar sclerosis
14	A. L.	Both	Autopsy	++++	Moderate	+++	Marked exudate	...	Pyelonephritis with multiple abscesses and malignant nephrosclerosis
15	B. W.	Left Right	Biopsy Autopsy	++++ ++++	All degrees All degrees	++++ ++++	Marked dilatation and atrophy; exudate Marked dilatation and atrophy; exudate	12	Chronic pyelonephritis; arteriolar sclerosis Chronic pyelonephritis; arteriolar sclerosis
16	F. C.	Right	Biopsy	++	All degrees	++++	Dilatation	25	Chronic pyelonephritis; arteriolar sclerosis
20	G. R.	Left	Biopsy	+	All degrees	++++	Marked, with exudate	60	Hydronephrosis; chronic and suppurative pyelonephritis; fibrosis and atrophy of kidney
21	A. L.	Left	Biopsy	++++	Moderate fibrosis	++	Marked, with atrophy	90	Hydronephrosis; chronic pyonephrosis; fibrosis and atrophy; arteriolar sclerosis
37	L. W.	Right Left	Autopsy Autopsy	++ ++	All degrees All degrees	None ++	Slight Dilatation	60 70	Arteriolar sclerosis Congenital cystic kidney and arteriolar sclerosis
38	H. A.	Right Left	Autopsy Autopsy	++++ ++++	Marked scarring Marked scarring	None +++	Dilatation and atrophy Marked inflammatory change	190 110	Arteriolar sclerosis Tuberculous cystic degeneration; arteriolar sclerosis
39	W. A.	Right Left	Autopsy Autopsy	++++ ++++	All degrees	++ ++++	Dilatation and atrophy, with pus	Arteriolar sclerosis Cystic degeneration with calcification; (?) tuberculosis
43	F. E.	Right Left	Autopsy Autopsy	++ ++	Slight Moderate	None ++++	Slight Dilatation and atrophy	70 40	Moderate arteriolar sclerosis Hydroneurter; scarring of kidney; arteriolar sclerosis
53	M. A.	Right	Biopsy	+	Slight	+	None	70	Hypoplasia; (?) pyelonephritis
*	E. K.	Right Left	Autopsy Autopsy	++++ ++++	Moderate All degrees	+++ +	Dilatation and atrophy Dilatation and atrophy	70 140	Polycystic kidney; arteriolar sclerosis Arteriolar sclerosis

* This case was not included in this series of "essential" hypertension because no records of blood pressure were available before the onset of renal failure.

Pathologic Anatomy of Kidneys.—Renal vascular disease was invariably associated with renal lesions of the varieties being considered in the available autopsy and biopsy material (table 8). This condition is also present in almost every instance of "essential" hypertension.¹⁶ When the renal disease was unilateral, there was always arteriolar sclerosis of the other kidney. Evidence of infection was not observed in every case, although scarring of the interstitial tissue was present in at least one kidney in all instances. The series is too small for further comment. Weiss and Parker^{11a} have recently pointed out the relation between pyelonephritis and disease of the renal blood vessels in instances of arterial hypertension; these cases offer further evidence of the association of renal disease and vascular changes in the kidneys.

Renal Disease and Other Classes of Hypertension.—In a previous report^{7b} a classification of "essential" hypertension was proposed, in which cases were grouped according to the presence of abnormalities involving four systems: renal, nervous, endocrine and arterial. Further investigation has served to identify more completely those belonging to the group of "renal" hypertension, as apart from the other three groups. In addition, renal lesions of minor degree were found in 11 of 32 patients exhibiting the "hypertensive diencephalic syndrome" (table 9). Twenty-two persons with mild hypertension were examined by urologic methods; renal abnormalities were found in 21, and in 2 hydronephrosis was marked (table 10). (The cases of these persons will be discussed in a later communication.)

It was found necessary to reclassify 2 of 11 cases previously classified as instances of "endocrine" hypertension and 2 of 12 classified as instances of "arteriosclerotic" hypertension because of the presence of organic renal disease discovered by urologic examination. These 4 cases were therefore placed in the group of "renal" hypertension; the existence of renal abnormalities was not previously known. Similarly, some disease of the kidneys was found in 50 of 52 cases considered "unclassifiable" until urologic examination disclosed disease unsuspected by ordinary methods of examination.

Clinical Characteristics of the "Renal" Group.—Certain clinical differences common to a majority of cases were found in this group. Eighty appeared to belong to the class of "renal" hypertension (table 11); in the remainder there was either only a slightly elevated blood pressure (21 cases) or certain clinical phenomena which placed them in the group of "nervous hypertension" (12 cases). Of the patients in these 80 cases, 37 are dead (table 12). It is of interest that failure of the kidneys or of the kidneys and the heart accounted for

16. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.* **13**:679, 1937.

TABLE 9.—*Hypertensive Diencephalic Syndrome*

Case No.	Name	Sex	Family History *	Age at Onset	Duration, † Years	Extremes of Blood Pressure ‡		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ¶	Urea Clearance, ¶ per Cent Normal	Present State, # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
81	A. B.	♀	+	25	4	220/140	150/100	0	0	Renal colic and hematuria at 20	1.025	114	L	Normal urogram
82 ††	B. H.	♀	++++	24	11	230/140	160/110	0	0	Toxemia of pregnancy	1.028	101	L	Slight bilateral hydronephrosis with UPJ obstruction
83	E. B.	♀	+	19	10	220/140	160/100	0	0	1.034	94	L	Ptoxis of right kidney; poor excretion of diodrast from left kidney
84	M. O.	♀	0	21	7	220/130	170/100	+	0	1.029	107	L	Slight bilateral hydronephrosis with UPJ obstruction
85	R. L.	♀	0	19	7	220/120	170/100	0	0	Occasional pain in right flank	1.033	112	L	Slight bilateral hydronephrosis with UPJ obstruction
86	S. F.	♀	+++	30	8	250/140	220/130	++	0	1.030	105	L	Left hydroureter
87	V. H.	♀	+	21	15	180/120	160/110	0	0	Toxemia of pregnancy	1.022	90	L	Slight right hydronephrosis with UPJ obstruction
88	J. P.	♀	+	42	10	230/140	200/120	+	0	1.029	110	L	Slight right hydronephrosis with UPJ obstruction and pyuria
89	T. L.	♀	+	33	8	225/140	160/110	0	0	1.029	107	L	High insertion of right ureter with slight obstruction
90	T. G.	♀	0	34	7	200/120	170/100	+	0	1.029	93	L	Calcification in right renal pelvis with diminished function; ureteral kink
91	A. Z.	♀	0	43	12	250/140	180/120	++	0	1.032	101	L	Slight right hydronephrosis with UPJ obstruction; double left kidney
92	A. S.	♀	++	47	14	190/120	150/90	++	0	1.025	98	L	Slight right hydronephrosis with UPJ obstruction

For interpretation of symbols not defined here, see table 1.
†† Case previously reported by Page and Heuer.¹³

TABLE 10.—*Mild Hypertension*

Case No.	Name	Sex	Family History*	Age at Onset	Duration,† Years	Extremes of Blood Pressure †		Ocular Fundi §		Renal Lesion At or Before Onset, Age	Maximal Urine Concentration ‖	Urea Clearance, ‖ per Cent Normal	Present State: # Cause of Death	Comment **
						High	Low	Arterio-sclerosis	Hemor-rhage and Exudate					
93	H. K.	♂	+	17	1	163/100	135/80	0	0	1.030	+	L	Bilateral hydronephrosis with UPJ obstruction
94	A. L.	♂	+	17	1	150/90	140/85	0	0	1.038	..	L	Slight right hydronephrosis with UPJ obstruction
95	E. B.	♂	+	16	5	180/90	140/60	0	0	1.033	133	L	Moderate right hydronephrosis with UPJ obstruction
96	B. B.	♂	+	20	2	180/100	150/90	0	0	138	L	Slight bilateral hydronephrosis
97	P. L.	♂	++	22	1	155/90	140/85	0	0	1.028	126	L	Right ptosis
98	M. S.	♂	+	33	1	160/110	130/90	+	0	1.026	..	L	Slight right hydronephrosis with UPJ obstruction
99	H. M.	♂	+++	29	7	160/100	140/90	0	0	1.022	..	L	Slight right hydronephrosis with UPJ obstruction
100	P. H.	♂	0	19	1	170/90	130/80	0	0	1.029	122	L	Bilateral double kidneys
101	G. H.	♂	+	17	1	155/90	130/80	0	0	1.028	123	L	No excretion of diodrast by left kidney; ptosis of right kidney
102	J. P.	♂	+	17	1	160/90	145/80	0	0	116	L	Marked right hydronephrosis
103	J. B.	♂	+	16	2	170/110	140/95	0	0	Albuminuria at 16	1.030	116	L	Slight bilateral hydronephrosis
104	P. Z.	♂	..	29	3	150/90	140/80	0	0	1.032	..	L	Slight left hydronephrosis
105	M. M.	♂	+++	34	5	170/120	140/70	0	0	1.032	111	L	Persistent pyuria with hemolytic staphylococcus
106	F. G.	♂	++	12	9	190/100	160/95	0	0	1.029	98	L	Slight right hydronephrosis and hydronephrosis
107	C. H.	♂	+	18	2	150/90	135/75	0	0	1.031	135	L	Moderate bilateral hydronephrosis
108	D. R.	♀	+	31	3	170/100	150/90	0	0	1.033	139	L	Slight ptosis of right kidney with UPJ obstruction; high insertion of left ureter
109	S. S.	♀	++++	34	3	150/100	135/95	0	0	1.029	81	L	Slight right hydronephrosis with UPJ obstruction
110	J. H.	♀	++++	50	12	180/100	150/85	+	0	1.025	120	L	Ptosis of left kidney; UPJ obstruction in right
111	P. M.	♀	++++	47	6	185/95	150/90	0	0	1.026	..	L	Ptosis of right kidney with UPJ obstruction
112	S. D.	♀	+++	28	10	170/105	140/95	0	0	1.029	..	L	Slight right hydronephrosis with UPJ obstruction
113	M. W.	♂	+	33	7	163/100	135/90	0	0	Calculus at 23; colic six times	1.022	116	L	Bilateral hydronephrosis with bilateral calculi in calices

For interpretation of symbols, see table 1.

death in 21 cases. A "malignant" course was common (17 cases), as were hemorrhagic and exudative lesions in the retina (38 cases). The level of the diastolic pressure was often high (average 126 mm. of mercury), while that of the systolic was comparably less elevated

TABLE 11.—*Summary of Renal Lesions in Eighty Cases*

Type of Lesion	Males		Females		All Patients		
	Living	Dead	Living	Dead	Total	Living	Dead
Obstruction.....	3	1	11	3			
Obstruction + calculus.....	1	1	..	1			
Obstruction + infection.....	4	1	7	1			
Obstruction + calculus + infection.....	..	1	25	26	9
Infection.....	1	0	2	4			
Infection + calculus.....	1	2	10	4	6
Calculus.....	1	4	5	1	4
Ptosis without obstruction.....	..	1	2	..	3	2	1
Miscellaneous unilateral lesions.....	5	2	2	..	9	7	2
Glomerulonephritis.....	..	6	..	2	8	0	8
Albuminuria before onset.....	..	6	6	0	6
Miscellaneous.....	3	1	4	3	1
Total.....	19	26	24	11	80	43	37

TABLE 12.—*Summary of Eighty Cases (tables 1 to 7)*

	Males		Females		Cases	
	Living	Dead	Living	Dead	Total	Per Cent
Number of cases.....	19	26	24	11	80	
Family history of hypertension.....	12	15	15	7	49	61
Average age at onset (years).....	34.8	34.5	28.5	28.5	32.3	
Greatest age at onset.....	58	50	55	45		
Lowest age at onset.....	21	17	19	21		
Average duration of disease (years).....	5.8	6.9	8.8	9.0	7.4	
Longest.....	17	30	33	16		
Shortest.....	½	½	1	½		
Extremes of blood pressure						
Average high.....	190/127	230/142	213/131	246/146	213/136	
Average low.....	164/109	197/120	178/113	204/128	183/116	
Highest individual level.....	220/160	260/190	300/160	270/170		
Lowest individual level.....	140/ 90	150/ 90	150/ 80	170/120		
Ocular fundi						
Presence of arteriosclerosis.....	4	14	10	5	33	42
Presence of retinitis.....	3	19	7	9	38	48
Mode of death						
Renal.....	..	9	..	6		
Cardiac and renal.....	..	4	..	2	21	69
Cardiac.....	..	4	..	2	6	
Cerebral.....	..	3	..	1	4	
Other and unknown.....	..	6	..	0	6	

(average 198 mm. of mercury). The blood pressures in these cases were generally stable and remained so during anesthesia induced by pentothal sodium. Cardiac enlargement was found in every case in which hypertension was prolonged. Renal function, while usually normal at first, often became diminished as the disease progressed. In other respects the patients in these cases resembled those commonly believed to be suffering from "essential" hypertension.

COMMENT

The nature of the association of organic renal diseases with hypertension has not been sufficiently defined. That association, however, must be common. In 1704 Baglivi¹⁷ reported the last illness of Marcellus Malpighi, who died in 1694 of apoplexy, aged 66, after suffering for many years of

. . . Vomitings, bilious Stools, Palpitations of the Heart, Stones in the Kidneys and Bladder, a pissing of Blood, and some light Touches of the Gout. Upon his coming to *Rome*, all these Disorders were inflam'd; especially the Palpitation of the Heart, the Stone in the Kidneys, and very sharp biting Night Sweats.

Malpighi then suffered apoplexy, with paralysis of the right side, and after forty days died of a second attack, which was ushered in by a recurrence of his renal stone. A description of the postmortem dissection follows:

The Heart was larger than ordinary, especially the Walls of the left Ventricle, which were as thick as the Breadth of two Fingers. . . . The left kidney was in a natural State, but the right was half as big again as the left, and the Bason of it was so much dilated, that one might easily thrust 2 Fingers into it. Perhaps this Dilatation of the Pelvis was the Occasion that as soon as the Stones were bred in the Kidneys, they presently slipt into the Bladder, and so sprung out from thence; which our excellent Friend had frequently own'd to me to be a Matter of Fact. In the Bladder we found a little stone that had descended thither four Days before the Invasion of the last Apoplectick Fit, and by its Descent exasperated his last Vertigoes. The rest of the natural *Viscera* were very well condition'd.

In the brain was found a massive hemorrhage.

In the original report of Richard Bright^{18a} were mentioned 2 cases probably similar to those which have been discussed. In both the left ventricle was hypertrophied; in 1 there were multiple renal calculi, and in the other only one kidney was markedly contracted. Bright later recorded 2 others in which also hypertrophy of the left ventricle and unilateral renal disease were observed.^{18b} The kidney in 1 case had been totally destroyed, leaving a sac filled with phosphates, while that in the other was markedly contracted and contained stones.

The significance of renal abnormalities is clear in those cases in which removal of a diseased kidney was followed by reduction in blood pressure. If improvement lasts for several months it is probable that the diseased kidney played a part in the genesis of hypertension. That

17. Baglivi, G., cited by Major, R. H.: *Classic Descriptions of Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 432-433.

18. Bright, R.: (a) *Original Papers of Richard Bright on Renal Disease*, edited by A. A. Osman, London, Oxford University Press, 1937; (b) *Cases and Observations Illustrative of Renal Disease Accompanied with Secretion of Albuminous Urine: Memoir the Second*, *Guy's Hosp. Rep.* 5:101, 1840.

the renal lesion is not the sole etiologic agent is shown by the fact that such a condition in the kidney often occurs without hypertension.

It seems, possible, therefore, that two separate factors are at work in these cases. One is a renal lesion; the other, perhaps a constitutional one, is unknown. Although singly each might not result in hypertension, together they may produce it. Opsahl¹⁹ has reached a similar conclusion regarding Bright's disease. The nature of this second (and possibly primary) factor may be hereditary (the patients in 64 per cent of these cases were known to have been descended from hypertensive persons, and the proportion is higher in certain groups), congenital or dependent on a specific internal derangement of the kidneys. The factor may be one of several. The work of Hines,²⁰ showing that persons hyperreactive to certain tests of vascular irritability were more common in families in which there was a hypertensive background, is interesting in this respect.

To call the condition here described "essential" is obviously erroneous, as "essential" hypertension has been defined as a condition in which there is no evidence of organic renal disease. The nature of the renal disease from which these patients suffered was discovered, however, only by special technics, as in most instances its presence was unsuspected. Although not "essential" hypertension, the disease resembles this condition exactly in its ordinary symptoms and signs, and can be defined only by careful examination.

Renal lesions associated with arterial hypertension have not been consistently found on postmortem examination, and the reason for this is unclear. Mild or moderate hydronephrosis might not be seen, unless the kidneys were fixed by injection of fixing fluid into the ureters. It is probable that many lesions change during the course of the superimposed vascular disease and are not recognizable after the kidneys have become contracted, as is sometimes the case with kidneys shrunk as a result of pyelonephritis. This study suggests that renal diseases associated with arterial hypertension can best be detected in the living patient before renal insufficiency has occurred.

There is some evidence that many diseases of the kidney are attended by reduction in renal blood flow. In the experimental animal increased intrapelvic pressure lowers the flow of blood through the kidney²¹; in man hydronephrosis results in reduction in the number and caliber of

19. Opsahl, R.: Zur Pathogenese der arteriellen Hypertension, unter besonderer Berücksichtigung der Rolle der Nieren und Nebennieren im Mechanismus des weissen Hochdrucks, *Acta med. Scandinav.*, 1938, supp. 92, pp. 1-262.

20. Hines, E. A., Jr.: The Hereditary Factor in Essential Hypertension, *Ann. Int. Med.* **11**:593, 1937.

21. Enger, R.; Gerstner, H., and Sarre, H.: Die Abhängigkeit der Nierendurchblutung vom Ureterendruck, *Zentralbl. f. inn. Med.* **58**:865, 1937.

blood vessels of the whole renal vascular tree.²² Vascular changes accompany chronic pyelonephritis, especially when the kidney is scarred.^{11a} The glomerular lesions of Bright's disease can be considered as resulting in partial renal ischemia. In certain cases of renal ptosis there may be obstruction to a vein, artery or ureter. The mechanism of arterial hypertension in persons exhibiting renal disease, however, remains speculative. In the experimental animal a large variety of renal lesions results in hypertension (sclerosis of the kidneys produced by roentgen rays,²³ chemical²⁴ and serum²⁵ nephritides, constriction of a renal vein,²⁶ ureteral ligation,²⁷ reduction of renal substance,²⁸ renal ischemia,⁵ capsular fibrosis induced by cellophane²⁹ and hydronephrosis.³⁰)³¹ There are also many renal diseases with renal insufficiency in man with which hypertension is associated and to which it is considered secondary (glomerulonephritis, urinary obstruction, polycystic disease, necrotizing nephroses, suppurative nephritis and pyelonephritis).

22. (a) Hinman, F., and Morrison, D. M.: Comparative Study of Circulatory Changes in Hydronephrosis, Caseo-Cavernous Tuberculosis, and Polycystic Kidney, *J. Urol.* **11**:131, 1924; (b) An Experimental Study of the Circulatory Changes in Hydronephrosis: Preliminary Report Relating to Unilobed Kidney as Instanced in the Rabbit, *ibid.* **11**:435, 1924. (c) Egger, K.: Die Veränderungen des Nierenarteriensystems in der Hydronephrose und ihre Beziehungen zur Nierenfunktion, *Ztschr. f. urol. Chir. u. Gynäk.* **44**:138, 1938.

23. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Experimental Nephritis Produced by Irradiation, *Am. J. M. Sc.* **172**:487, 1926.

24. Arnott, W. M., and Kellar, R. J.: The Effect of Renal Denervation on the Blood Pressure in Experimental Renal Hypertension, *J. Path. & Bact.* **42**:141, 1936.

25. Arnott, W. M.; Kellar, R. J., and Matthew, G. D.: Hypertension Associated with Experimental Serum Nephritis, *Edinburgh M. J.* **44**:205, 1937.

26. Pedersen, A. H.: A Method for Producing Experimental Chronic Hypertension in the Rabbit, *Arch. Path.* **3**:912 (May) 1927.

27. Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, *Tr. A. Am. Physicians* **51**:280, 1936.

28. (a) Chanutin, A., and Barksdale, E. E.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: Relationship of Left Ventricular Hypertrophy, Width of Cardiac Muscle Fiber and Hypertension in Rat, *Arch. Int. Med.* **52**:739 (Nov.) 1933. (b) Wood, J. E., Jr., and Ethridge, C.: Hypertension with Arteriolar and Glomerular Changes in Albino Rat Following Sub-Total Nephrectomy, *Proc. Soc. Exper. Biol. & Med.* **30**:1039, 1933.

29. Page, I. H.: A Method for Producing Persistent Hypertension by Cellophane, *Science* **89**:273, 1939.

30. Williams, J. R., Jr.; Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, *Arch. Int. Med.* **62**:805 (Nov.) 1938.

31. Chronic hypertension has been induced in rats by explantation of one ureter. This results in moderate hydronephrosis in the affected kidney. Hypertension sometimes follows trauma to one kidney in rats. These methods will be reported by one of us (H. A. S.).

The mechanisms of these forms of hypertension are unknown, but the role of the kidneys in their production seems established. The frequency of arterial hypertension in cases of prostatic obstruction is well understood, and these two conditions often occur in the *absence* of renal insufficiency.³² There is no doubt that the elevation of blood pressure is caused by the obstruction, for when relief follows surgical intervention, hypertension often disappears. Such cases, were it not for the urinary symptoms, might easily be confused with those of "essential" hypertension.

The large number of cases of arterial hypertension in which there is organic renal disease or a probability of it is evidence for its significance. The importance of minor abnormalities indicating stasis in the renal pelvis or increased intrapelvic pressure is less clear, although such lesions are much more common in cases of arterial hypertension than in cases of normal persons. In Campbell's series³³ congenital ureteral obstruction was present once in 138 children, and Eisendrath³⁴ found that aberrant renal arteries of a nature which could be considered a potential cause of obstruction were present in about 5 per cent of all kidneys. Such arteries have already been found in 12 cases of hypertension in this series, and their presence has been suspected in many others.

Arteriolar sclerosis as well as the renal abnormality is found in the kidneys in these cases. Two suppositions can be drawn from this association: one, that arteriolar disease is a separate condition on which hypertension is dependent, the renal lesion being incidental, and the other, that the renal lesion itself causes renal damage and hypertension and initiates arteriolar sclerosis in both kidneys. The latter view seems more tenable in the light of the work of Wilson and Byrom,³⁵ who were able, in rats, to produce arteriolar disease in one kidney when the artery of the other was partially constricted.

Distinction has been drawn between cases of this nature and those in which hypertension with renal insufficiency was exhibited. Arterial hypertension associated with renal disease without renal failure has not been sufficiently emphasized as a clinical entity. Although some factor

32. (a) Young, H. H.: *Surgery of the Prostate*, in Nelson Loose Leaf Living Surgery, New York, Thomas Nelson & Sons, 1928, vol. 6, p. 161. (b) O'Connor, V. J.: *Observations on the Blood Pressure in Cases of Prostatic Obstruction*, Arch. Surg. **1**:359 (Sept.) 1920; (c) *Further Observations on the Blood Pressure in Cases of Urinary Obstruction*, J. Urol. **10**:135, 1923.

33. Campbell, M. F.: *Pediatric Urology*, New York, The Macmillan Company, 1937, vol. 1.

34. Eisendrath, D. N.: *Hydronephrosis Due to Obstruction of the Renal Pelvis by One of Two Main Renal Arteries*, J. Urol. **24**:173, 1930.

35. Wilson, C., and Byrom, F. B.: *Renal Changes in Malignant Hypertension: Experimental Evidence*, Lancet **1**:136, 1939.

other than the renal disease probably exists in cases of this condition, it is nevertheless justifiable to designate the disorder as "renal" (or perhaps "urologic") hypertension; the evidence is in favor of a renal element being important.

In 113 (45 per cent) of 250 cases of so-called essential hypertension patients were found to suffer from organic renal disease, of many varieties and degrees of severity. This incidence is extraordinarily large. It must be stated that the patients, the subjects of this study, belonged usually in the younger age groups, hypertension having developed in 62 per cent before the age of 40. Renal lesions were by no means confined to young persons, however; they were found in 22 in whom the onset of hypertension occurred after 40 and in 20 others who were over 40 when the nature of the lesions was discovered, 18 being older than 50. There is reason to believe that these lesions, while more common in young persons, may be found at all ages if careful search for their presence is made.

Of great value for the disclosure of renal lesions was the study of the renal pelves in roentgenograms made after the intravenous injection of diodrast (excretory urography), which established their presence in 71 of 178 cases. Postmortem examinations were of value in only 16 cases, the history in 20 and other procedures in 6. These results emphasize the importance of the utilization of all methods of examination for renal disease in patients exhibiting elevation of the arterial pressure. Examples of this association are being found in urologic clinics.³⁶

This study has been rewarding in that it has drawn attention to the prevalence of organic renal disease of many varieties associated with arterial hypertension. That in all these cases the hypertension was called "essential" before the renal lesions were found is further evidence that "essential" hypertension is not a single disease.

SUMMARY

Two hundred and fifty cases of so-called essential hypertension have been studied with a view to ascertaining the presence of organic renal disease. One hundred and seventy-eight have been especially studied as regards the genitourinary tract. Evidence of renal disease of a nature not usually considered to be dependent on hypertension has been found in 113 cases.

CONCLUSIONS

Organic renal disease is a common occurrence in cases of so-called essential hypertension. Examination of the genitourinary tract for

36. Maher, C. C., and Wosika, P. H.: Urologic Hypertension: A Study of One Hundred and One Cases, *J. Urol.* **41**:893, 1939.

abnormalities is an important part of the study of cases of hypertension. A history of renal disease often antedates the onset of arterial hypertension, even when no abnormality can be found. There is justification for regarding the condition in these cases no longer as "essential" hypertension but as a different disease.

REPORT OF ELEVEN CASES

CASE 1.—The case of P. M., a 29 year old clerk, has been reported previously.¹³ He was first admitted to the Hartford Hospital in June 1932 because of recurrent attacks of pain in the left flank, of three months' duration. Cystoscopic examination and roentgenograms taken after injection of the ureters with a contrast medium (retrograde pyelograms) revealed a calculus in the left renal pelvis; slight hydronephrosis and angulation of the ureter at the ureteropelvic junction were also present. He was reexamined in July 1934 for the same complaint, and the stone was seen to be larger and to occlude the middle and lower calices of the pelvis. The stone was removed at operation. His systolic blood pressure was then 125 and his diastolic 80 mm. of mercury. In November 1934 he was readmitted because he complained of headaches, nocturia and dimness of vision. His systolic blood pressure was 210 and his diastolic 140 mm. of mercury. There was marked albuminuria and diminution of renal function. When he entered the hospital of the Rockefeller Institute in March 1935 his renal function was found to be normal. Section of the anterior nerve roots resulted in considerable improvement.

A renal calculus was present in the pelvis of the kidney for two years. There were angulation of the ureter at the ureteropelvic junction and slight hydronephrosis. Arterial hypertension became manifest four months after removal of the calculus.

CASE 9.—R. K. was a 40 year old mechanical engineer. His mother suffered from high blood pressure and apoplexy. Severe "quinsy," at the age of 37, was the only illness he remembered to have had. At the age of 34 he suffered an attack of left-sided renal colic associated with hematuria, and he passed a small calculus after a similar attack at the age of 36. Cystoscopic examination at the time showed no abnormality. His blood pressure was known to have been normal at the ages of 34, 36 and 37. At 38, however, it was slightly elevated, but he was able to obtain life insurance after complete examination; at the age of 39 it was definitely elevated, and albumin was found in his urine. He was first examined in this clinic at the age of 40, complaining of dyspnea and slight headache.

In October 1938 his heart was found to be enlarged. Incomplete left bundle branch block was evident in the electrocardiogram. In the ocular fundi were perivasculitis, several areas of white exudate and slight papilledema. The maximal specific gravity of the urine was 1.017.³⁷ The clearance of urea³⁸ was 44 per cent of normal. There was no increase in the nitrogen content of the blood. His arterial pressure varied between 250 and 220 mm. of mercury systolic and 160 and 140 mm. diastolic.

37. The nonprotein specific gravity of the urine after a period of at least twenty-four hours of restricted fluid intake.

38. By clearance of urea is meant that determined by the method of Van Slyke.

Pyelograms after intravenous injection³⁹ exhibited an apparently normal renal pelvis on the right side, but the pelvis on the left was not seen. Cystoscopic examination was therefore made, and retrograde pyelograms showed a filling defect in the middle calix of the left renal pelvis (fig. 1 *A*). The outline of the left kidney was small and irregular. Measurement of the function of each kidney showed that the left kidney was relatively deficient.

	Left	Right
Phenolsulfonphthalein excretion (25 min).....	0	5.2%
Clearance of urea ⁴⁰	8%	29%

His condition rapidly became more grave. Dyspnea at night and on exertion appeared, and headache was a distressing symptom. He died in January 1939, of renal failure.



Fig. 1.—*A*, retrograde pyelogram (case 9). There is a small filling defect in the middle calix of the functionless left kidney. *B*, retrograde pyelogram (case 12), showing distortion of the right renal pelvis with angulation of the ureter at the ureteropelvic junction.

39. Pyelograms after intravenous injection were made in the following manner: Patients were prepared by rigid restriction of fluids for thirty-six hours before the examination. Diodrast was injected and roentgenograms made of the abdomen five and fifteen minutes after the end of the injection. The patient was then instructed to drink water until urine was passed, and photographs were taken periodically until the renal pelvis appeared clear of the injected substance.

40. Measurements of the clearance of urea made separately from each kidney are subject to errors, but are relatively comparable. Similar catheters (no. 6 F in most instances) were used. As many specimens were obtained as was consistent with the comfort of the patient, and measurements were made on each, the average being taken. The usual determination was made on two or three fifteen minute specimens.

Severe hypertension followed attacks of left-sided renal colic, one of which was accompanied by the passage of a stone. The left kidney was found to be small and irregular in outline on roentgen examination and to be functioning poorly. There was already some diminution of function of the other. The clinical appearance was that of "malignant" hypertension. The exact nature of the disease in the affected kidney is unknown.

CASE 12.—M. F., a 37 year old housewife, had suffered from hypertension for eight years. There was no history of elevated blood pressure in her family. Her first pregnancy, at the age of 21, was accompanied by severe pyelitis, and an "abscess of the kidney," which disappeared after childbirth, was said to have been present. She suffered from recurrences of pyelitis on several occasions, until the age of 28. Her second pregnancy was uneventful, but her third, at the age of 25, was accompanied by considerable nausea and vomiting. Her fourth, at the age of 28, was uneventful until the twenty-eighth week, when her systolic pressure rose to 170 and her diastolic to 110 mm. of mercury and edema and albuminuria appeared. She then began to suffer with headaches, convulsive seizures and syncope attacks at intervals of three weeks. In the thirty-fifth week of the pregnancy she was admitted to Fordham Hospital, acutely ill of pulmonary edema. There were marked albuminuria, elevation of nonprotein nitrogen in the blood and edema of the extremities and face. She was delivered of stillborn twins, and a few hours later a second attack of pulmonary edema developed. Her systolic pressure was 220 and her diastolic 160 mm. of mercury. The ocular fundi showed the lesions of hypertensive retinitis. Her arterial pressure fell slowly during the following month to a level of 140 mm. systolic and 90 mm. diastolic, but during the next two years it again became elevated. She began to suffer convulsive seizures associated with severe headaches at the age of 30; her systolic pressure was said to have been 310 mm. of mercury during such an attack. She was first admitted to this hospital in August 1936.

Physical examination then revealed little of significance. The heart did not appear enlarged in roentgenograms. The ocular fundi showed some tortuosity of the vessels. The tendon reflexes were hyperactive. The systolic pressure varied from 248 to 190 mm. of mercury and her diastolic from 154 to 120 mm. during two months of observation. The clearance of urea was 68 per cent of normal, and the maximal specific gravity of the urine was 1.027. There was no albumin or abnormal microscopic elements in the urine.

During the next two years there occurred attacks of cardiac pain, which was relieved by glyceryl trinitrate. The convulsive seizures recurred a number of times, and each was associated with spasticity of the right side. Her systolic blood pressure varied under observation from 270 to 220 mm. of mercury and her diastolic from 160 to 128 mm. The maximal specific gravity of the urine remained at 1.025, and the clearance of urea varied from 73 to 125 per cent of normal. A trace of albumin appeared in the urine, and the T waves of the electrocardiogram became inverted. Pyelograms after intravenous injection of a contrast medium

The results were calculated in a manner which set the normal at 50 per cent for each kidney. When the corrected volume of urine was 1 cc. per minute or more, clearances were calculated as maximal. The excretion of phenolsulfonphthalein after intravenous injection of 1 cc. of the dye was measured on the same samples of urine. Under the conditions of cystoscopic examination, it has been found that the function of kidneys may tend to be lower than normal.

demonstrated a movable left kidney, and the renal pelvis on the right side was seen to be distorted (fig. 1 *B*). In October 1938 cystoscopic examination was performed at the New York Hospital. Retrograde pyelograms showed a distorted right renal pelvis with an angulation at the ureteropelvic junction. Separate specimens from the two kidneys were obtained after the intravenous injection of phenolsulfonphthalein. This dye appeared from the left ureteral catheter in two minutes, and 46 per cent of the amount injected was excreted in thirty minutes. It appeared from the right side in five and a half minutes, and only 13 per cent was excreted. Cystoscopic examination was again performed on Oct. 3, 1939, and the functions of the two kidneys, determined separately, were as follows:

	Left	Right
Phenolsulfonphthalein excretion (30 min.).....	9.1%	5.4%
Clearance of urea.....	26.0%	14.0%
White blood cells.....	Few	Moderate number in clumps

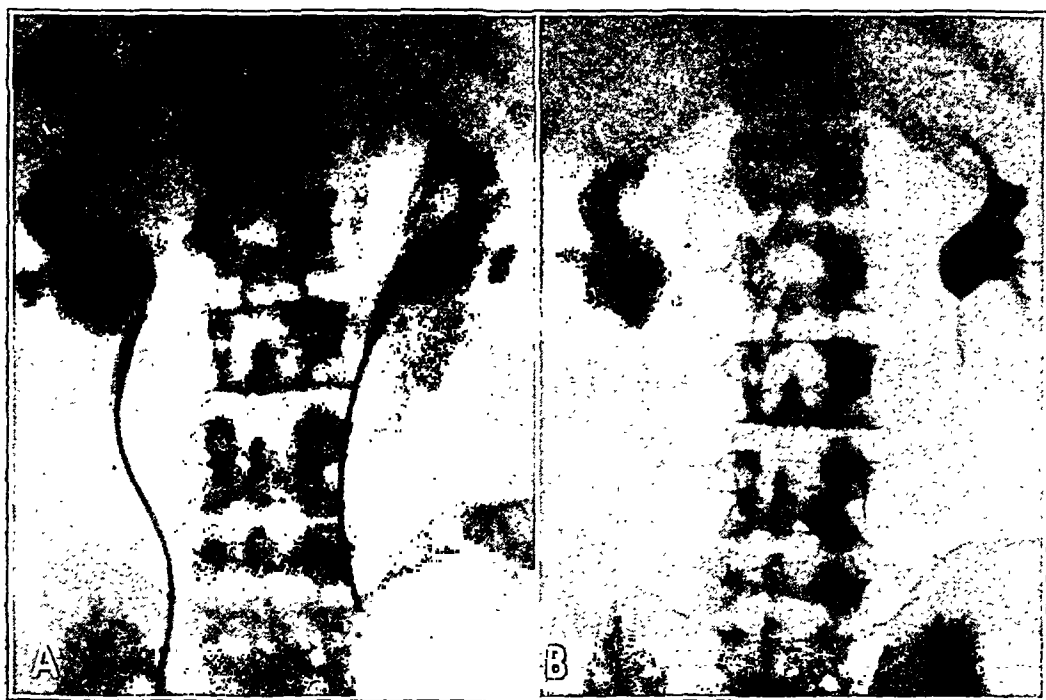


Fig. 2 (case 19).—*A*, retrograde pyelogram. *B*, pyelogram after intravenous injection of a contrast medium. Note the bilateral hydronephrosis with angulation of the ureters at the ureteropelvic junctions. Distention of the pelvis under pressure produced greater dilatation than when the radiopaque medium was excreted by the kidney.

She continues to suffer from severe headaches, convulsive seizures and frequent attacks of cardiac pain and is almost totally incapacitated by her illness.

Arterial hypertension began during a pregnancy in which "toxemia" developed. Previous to this were many attacks of "pyelitis." Hypertension, now of nine years' duration, is severe. The right kidney functions poorly, and there are obstruction at the ureteropelvic junction and distortion of the renal pelvis. The course is that of "essential" hypertension.

CASE 19.—J. G., a man aged 31, has been reported on in a previous communication.^{7b} Albuminuria had been present for many years, and hypertension began at the age of 21. Bilateral hydronephrosis, with angulation of both ureters at the ureteropelvic junction, was discovered in January 1938. Retrograde pyelograms showed well marked hydronephrosis on the right and moderate on the left (figs. 2*A* and *B*). Determinations of the function of each kidney were as follows:

	Left	Right
Phenolsulfonphthalein excretion (68 min.).....	21.0%	19.4%
Clearance of urea.....	67.6%	58.7%
White blood cells	0	+

Hydronephrosis of well marked degree was present without diminution of renal function as measured by these methods. This lesion was associated with arterial hypertension.

CASE 22.—E. Z., a 58 year old housewife, had no evidence of hypertension in her family. At 26 her uterus and ovaries were removed and her menses ceased. She had suffered from frequent attacks of tonsillitis until her tonsils were removed, at the age of 37. When she was 43 albumin was found in her urine by a life insurance examiner; albuminuria persisted for the next three years. Her blood pressure was said to have been normal at that time but was found to be elevated at the age of 45. An operation on her sinuses was performed at age 48. She complained of no symptoms until the age of 50, when palpitation and dyspnea on exertion appeared. She was first seen in this clinic at the age of 52. Her heart was then slightly enlarged on roentgen examination. There was thickening of her peripheral arteries. The ocular fundi showed a moderate amount of tortuosity and thickening of the arteries, with irregularity in their caliber. A few small scars, the sites of hemorrhages discovered a year previously, were seen. The maximal specific gravity of the urine was 1.030. Measurements of the clearance of urea varied from 78 to 50 per cent of normal. There was no albuminuria, but a few casts and many white blood cells were found in the urine. Her systolic pressure varied from 190 to 166 and the diastolic from 120 to 104 mm. of mercury.

She was seen at frequent intervals during the next six years. At the age of 56 she complained of a continuous ache in the right flank, lasting several months. At 57 she first began to complain of precordial pain, which radiated down the left arm. This became more severe, and at the age of 58 she was partially incapacitated by it. The pain was relieved by glyceryl trinitrate. She suffered three attacks of acute pulmonary edema. Her blood pressure became higher, the systolic varying between 234 and 186 and the diastolic between 140 and 120 mm. of mercury. The clearance of urea was 56 per cent of normal, and the maximal specific gravity of the urine was 1.023. There was a small amount of albumin in the urine, with many white blood cells. Pyelograms after intravenous injection of a contrast medium showed a calculus in the upper calix of the right kidney, the calix itself being dilated and club shaped. On the left side little of the radiopaque medium was excreted, but a diffuse, rounded shadow was seen superimposed on the shadow of the kidney, suggesting a large hydronephrotic sac. Cystoscopic examination was not performed because of the patient's condition. Cardiac pain became more severe, and she died, suddenly, in her sleep, in January 1939.

Hypertension was of fifteen years' duration. It was preceded by albuminuria and accompanied by left hydronephrosis and right renal calculus. The course was indistinguishable from "essential" hypertension, with cardiac pain a prominent symptom.

CASE 24 (previously reported¹³).—P. S., a 30 year old housewife, had suffered from hypertension since March 1934, although her blood pressure had been slightly elevated since May 1931. She has been seen in this hospital at regular intervals during the past five years. Anterior root section, performed in October 1934, resulted in lowering her blood pressure for eighteen months. Her systolic pressure during the past three years has varied from 220 to 180 and her diastolic from 115 to 140 mm. of mercury. There has been a tendency during the past year toward a higher level. The maximal specific gravity of the urine was usually 1.023, and the clearance of urea has varied from 165 to 115 per cent of normal. The heart has become slightly enlarged. Pyelograms after intravenous injection of a contrast medium showed slight dilatation of the right renal pelvis, with retention of the



Fig. 3.—*A*, retrograde pyelogram (case 24) showing bilateral hydronephrosis. *B*, pyelogram (case 28) after intravenous injection of a contrast medium, showing marked renal ptosis.

radiopaque material for two hours. Cystoscopic examination was performed in February 1939. Retrograde pyelograms demonstrated moderate bilateral hydronephrosis, greatest on the right, with angulations at the ureteropelvic junction (fig. 3 *A*). The upper calix of the right renal pelvis was blunted. Studies of the function of each kidney gave the following results:

	Left	Right
Phenolsulfonphthalein excretion (30 min.).....	26%	11%
Clearance of urea.....	71%	32%

Arterial hypertension was associated with bilateral hydronephrosis of moderate degree. The right kidney showed diminished function, while that of the left kidney was increased, the total excretion being normal.

CASE 28.—The case of M. B., a 33 year old nurse, has been reported.⁴¹ For ten years she had suffered from attacks of pain in her right flank, apparently caused by marked right renal ptosis and relieved by cystoscopic manipulation (fig. 3 B). For nine years she had exhibited elevation of blood pressure, which varied during the past five years from 240 to 180 mm. of mercury systolic and 135 to 100 mm. diastolic. The maximal specific gravity of the urine and the clearance of urea had remained within normal limits, and there had occurred no signs of severe damage to her heart or kidneys. Cystoscopic examination was therefore performed in October 1938, and measurements of the clearance of urea and the excretion of phenolsulfonphthalein were made on specimens from each kidney. The results were as follows:

	Left	Right
Phenolsulfonphthalein excretion (10 min.).....	12.1%	2.9%
Clearance of urea.....	88%	21%

This procedure was repeated in February 1939, with the following results:

	Left	Right
Phenolsulfonphthalein excretion (75 min.).....	34.8%	16.1%
Clearance of urea.....	53%	28%

Arterial hypertension was associated with unilateral renal disease, which probably preceded the elevation of blood pressure. There was normal renal function as measured by ordinary procedures, but marked ptosis with diminished function was present in one kidney. The clinical appearance was typical of benign "essential" hypertension.

CASE 39.—W. A., a 37 year old insurance broker, had a history of hypertension in his family, his maternal grandmother having died as a result of it. He had always enjoyed good health, but at the age of 7 albumin was found in his urine, and on numerous subsequent occasions it was said to have been present. At the age of 28 his systolic pressure was found to be 140 mm. of mercury, and he was unable to procure a license as an aviator. At the age of 33 he began to suffer severe headaches, and at 34 his systolic pressure was found to be 180 and his diastolic 120 mm. of mercury, both having previously been only slightly above normal.

When seen in January 1935, at the age of 35, his systolic pressure was 172 and his diastolic 110 mm. of mercury. His heart was slightly enlarged. The ocular fundi were normal. The clearance of urea was 90 per cent of normal. There was slight albuminuria. Two months later the clearance of urea had fallen to 49 per cent of normal, and the maximal specific gravity of the urine was 1.015. The level of the blood pressure had not changed. At the age of 36 his systolic pressure was 172 and his diastolic 140 mm. of mercury. At 37 his systolic pressure was 200 and his diastolic 144 mm., the clearance of urea had fallen to 27 per cent and there was retention of nitrogen in the blood. Hemorrhages and exudates appeared in his ocular fundi. Six months later symptoms of heart failure set in, and the clearance of urea had decreased to 6 per cent.

Cystoscopic examination had been performed by Dr. M. Boyd, of Atlanta, Ga., in April 1937. On the left side it was impossible to pass a ureteral catheter. Roentgenograms showed slight hydronephrosis, with angulation of the uretero-pelvic junction on the right. The left kidney was not seen, and there were several

41. Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, *Am. J. M. Sc.* **199**:601, 1940.

large rounded shadows of the density of calcium in this area, which resembled calcified cysts (fig. 4 *A*).

He died in October 1937, of uremia complicated by bronchopneumonia. Post-mortem examination disclosed that the right kidney was shrunk and granular, and on microscopic section lesions typical of severe arteriolonephrosclerosis were seen. The left kidney was almost completely replaced by a multilocular cyst, which was partly calcified. A few distorted remnants of renal tissue showed the lesions of severe arteriolar sclerosis. The heart was enlarged, and there was fibrinous pericarditis.

Albuminuria had been present since childhood. Hypertension, at first mild, became severe at the age of 34. The patient died of uremia.

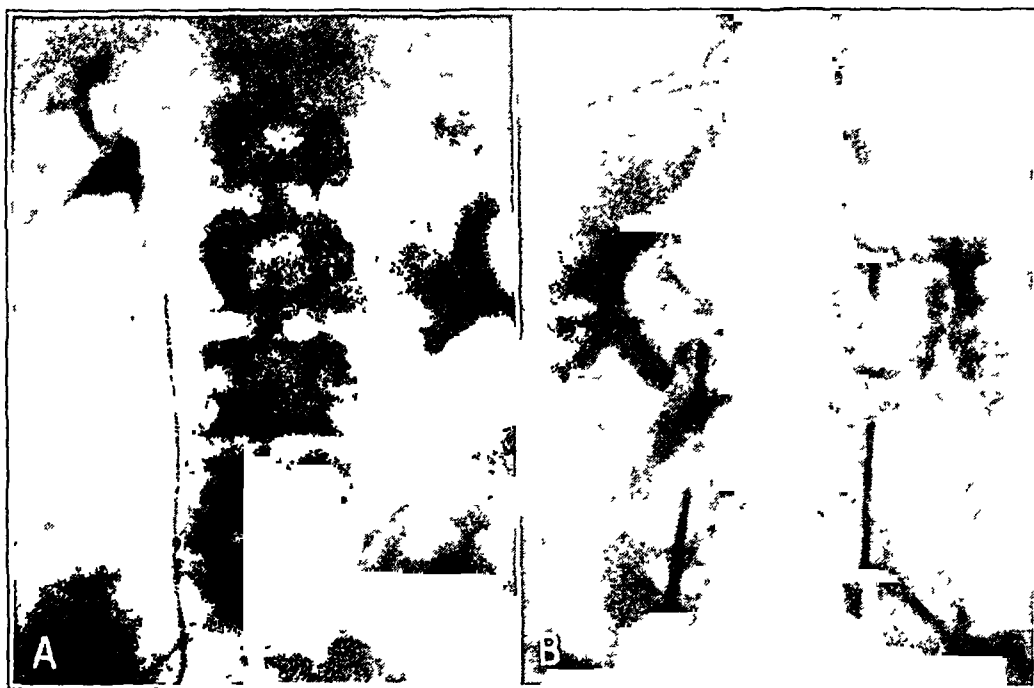


Fig. 4.—*A*, retrograde pyelogram (case 39). The left ureter was obliterated and the kidney replaced by a calcified cyst. Some degree of obstruction appears to be present on the right side. *B*, retrograde pyelogram (case 54) showing sharp angulation of the right ureter.

A functionless left kidney was found. The association of these three conditions appears significant.

CASE 41.—L. L. was a 54 year old broker. His father died at 77, of apoplexy, and his mother at 59, of Bright's disease. He enjoyed excellent health until the age of 44, when he suffered an attack of "lumbago" and received treatments with a sun lamp. During one treatment he fell asleep and burned himself badly. After this he suddenly became blind and was taken to a hospital. He was unconscious for five days. His blood pressure became elevated to 220 mm. of mercury systolic; he suffered attacks of pulmonary edema, and nitrogenous elements in the blood were said to have increased. He was discharged with the diagnosis of "acute nephritis with uremia." Albuminuria lasted six months and then disappeared, and his blood pressure fell to a level just above normal. Hypertension was next dis-

covered at the age of 50, when he suffered a mild attack of left hemiplegia for three weeks. Weakness of the left side and occasional dizzy spells have been his only complaints since then.

On physical examination in February 1937 there was slight weakness of the whole left side, including the face, with accentuation of the deep reflexes. The peripheral vessels were slightly thickened, and those in the ocular fundi were tortuous. The heart was slightly enlarged in roentgenograms. The maximal specific gravity of the urine was 1.028. There were a trace of albumin in the urine and occasional red blood cells in the sediment. The clearance of urea was 102 per cent of normal. Pyelograms after intravenous injection of a contrast medium were normal. His systolic blood pressure varied from 184 to 170 and his diastolic from 130 to 118 mm. of mercury. He lives an active life and has few complaints.

Hypertension followed an attack of renal damage, apparently induced by a severe burn. Renal function subsequently became normal. Left hemiplegia occurred some time later. The appearance is typical of "essential" hypertension in an older person.

CASE 54.—M. A., a 33 year old nurse, had suffered from hypertension for thirteen years. Her brother had sustained an apoplectic stroke at 40, and his blood pressure was known also to have been elevated for thirteen years. A mild attack of scarlet fever at 11, pneumonia at 12, an appendectomy at 25 and a number of operations on her nose and throat were important episodes in her history. At the age of 20, while at college, she had occasional headaches. Her systolic blood pressure was found to be 180 to 200 and her diastolic 110 mm. of mercury. There was a trace of albumin in her urine, which soon disappeared. Her blood pressure fluctuated during the next six years from normal to its former level. After the appendectomy, at the age of 25, an infection of the urinary tract developed, which lasted several weeks. Since then she has complained at times of burning on urination, frequency and slight pain in the right flank. There have been few symptoms referable to hypertension.

In September 1935 physical examination revealed little of importance. The ocular fundi were normal. The heart was slightly enlarged in roentgenograms. Her systolic pressure varied from 210 to 200 and her diastolic from 132 to 120 mm. of mercury. The maximal specific gravity of the urine was 1.026, and the clearance of urea was 149 per cent of normal. There was no albuminuria. Various changes have occurred during the past three years. Her systolic pressure has varied from 210 to 225 and her diastolic from 130 to 156 mm. of mercury. The vessels of the ocular fundi have become somewhat thickened and tortuous. Further enlargement of the heart has occurred, and the T waves in the electrocardiogram have become inverted. Renal function, however, has remained good, the maximal specific gravity of the urine varying between 1.033 and 1.029. Pyelograms, made in February 1938, after intravenous injection of a contrast medium, showed an angulation of the ureter on the right, without hydronephrosis (fig. 4 B). The kidney was movable and ptosed. This angulation was well demonstrated by retrograde pyelograms. The functions of the two kidneys were as follows:

	Left	Right
Phenolsulfonphthalein excretion (10 min.).....	7.4%	3.5%
Clearance of urea.....	59%	26%

Because of repeated attacks of pain in the right side she was treated with ureteral dilatation by another physician.

Arterial hypertension, of thirteen years' duration, was associated with angulation of one ureter and diminution of renal function of the associated kidney. There had been infection of the urinary tract after the onset of hypertension.

CASE 78.—A. B., a 41 year old salesman, began to complain of severe headaches at the age of 29. His father died of lead poisoning; his mother, who suffered from hypertension, of apoplexy. He had always been of a high-strung, nervous disposition. His tonsils were removed at 22 and his appendix at 25 years of age. His systolic pressure was 130 to 135 mm. of mercury at the age of 22, but at 29 it was found to be 160 mm. with a diastolic pressure of 90 mm. Renal function at that time, calculated with the Van Slyke coefficient, was normal. There was no albuminuria or abnormal formed constituents in the urine. At 32 he suffered a "nervous breakdown." His headaches continued. A number of minor operations on his sinuses were undertaken for relief of these, without relief. His blood pressure was labile during the next few years, at times mounting to 250 mm. of mercury systolic and 120 mm. diastolic, with minimal albuminuria and no abnormal formed elements in the urine. At the age of 37, after he had prolonged rest in bed, it fell to 170 mm. of mercury systolic and 120 mm. diastolic, but rose immediately after that and remained constant at about 240 mm. systolic and 130 to 140 mm. diastolic. At the age of 38 the pituitary and adrenal glands were given roentgen radiation, without change in the level of his blood pressure or in his symptoms. At 39 bilateral splanchnic resection was performed, followed by temporary reduction in the level of the blood pressure.

It seemed at the age of 40 that his disease was progressing rapidly. His systolic pressure varied between 280 and 230 mm. of mercury and his diastolic between 160 and 140 mm. In the ocular fundi there were papilledema, perivascularitis, tortuosity of the vessels, with white exudate, and a number of scattered hemorrhages. The heart was slightly enlarged. The peripheral vessels were slightly thickened. The clearance of urea was 76 per cent of normal. There was gross hematuria, for which no cause was found on cystoscopic examination. During the next seven months his blood pressure remained at the same level, and the urea clearance dropped rather rapidly to 15 per cent of normal, with elevation of the urea nitrogen of the blood to 36 mg. per hundred cubic centimeters. Then, in succession, came attacks of cerebral symptoms and of pulmonary edema, of which he died. The diagnosis at autopsy was chronic glomerulonephritis, generalized arteriosclerosis and hypertrophy of the heart. The splanchnic nerves, above the diaphragm, were found to have been completely removed.

A case of a patient with arterial hypertension is described to which the causal relation of Bright's disease is unknown. The clinical appearance was typical of "essential" hypertension. He died of renal and cardiac failure. His kidneys showed changes typical of chronic glomerulonephritis.

Dr. George W. Fish and Dr. Herbert B. Traut gave advice regarding the interpretation of roentgen photographs of the urinary organs. Dr. John H. Robinson performed the cystoscopic examinations. Miss Tilla Hefter gave technical assistance.

THE BLOOD PICTURE IN CHICKENPOX

ARTHUR ANDREWS HOLBROOK, M.D.

MILWAUKEE

The blood picture in chickenpox has received little attention in textbooks on pediatrics. The discussion in "The Diseases of Infants and Children" by Griffith and Mitchell¹ is exceptional. Furthermore, one could not learn much of the subject from books on hematology until Downey² reviewed the literature, in 1938. Other surveys had previously appeared in various articles, notably those by Ciuca, Tudoranu and Francke,³ Vitetti⁴ and Salvadei.⁵ These authors also added their own contributions. It is quickly evident from these accounts that a typical blood formula for varicella has not yet been described. Indeed, so many different findings have been recorded that the words written by Da Costa⁶ thirty-five years ago may well be repeated today, "It is obvious that the contradictory reports of various observers must be reconciled by further investigation before the blood examination in varicella can have any dependable clinical bearing."

There are a number of reasons for desiring a more definite idea of the reaction of the blood in chickenpox. If one could establish the regular occurrence of a characteristic sequence of changes before the infectious stage of the disease, it might be a ready means for apprehending cases before appearance of the rash or for determining the absence of infection in nonimmune contacts during the assumed incubation period. Second, since the relation between varicella and herpes zoster is still obscure and since generalized herpes zoster is held by some to be identical with chickenpox, it would help clarify these problems to know the blood pictures typical of both conditions. Finally, a leukemoid lymphatic reac-

1. Griffith, J. P. C., and Mitchell, A. G.: *The Diseases of Infants and Children*, ed. 2, Philadelphia, W. B. Saunders Company, 1937.

2. Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 4, pp. 2666-2667 and 2685-2686.

3. Ciuca, M.; Tudoranu, G., and Francke, M.: *Contribution à l'étude de sang dans la varicella*, *Compt. rend. Soc. de biol.* **98**:623-625 (March 9) 1928.

4. Vitetti, G.: *Stato degli organi ematopoietici nella varicelli*, *Pediatria* **36**: 1107-1113 (Oct. 15) 1928.

5. Salvadei, A.: *Contributo alla variazioni della formula ematologica nella varicella iniziale*, *Clin. pediat.* **11**:1048-1060 (Nov.) 1929.

6. Da Costa, J. C., Jr.: *Clinical Hematology*, Philadelphia, P. Blakiston's Son & Co., 1905.

tion has been described by Goldman⁷ in a case of chickenpox, and I⁸ have reported 1 case and collected others from the literature representing the coincidence of chickenpox and lymphatic leukemia. Although cases of such associated conditions are rare, the possibility must always be considered, and complete understanding of the normal blood picture in chickenpox would greatly aid in making the differential diagnosis.

An epidemic of chickenpox occurring in Milwaukee County in the fall of 1939 offered an opportunity for making the study herein described. Since the majority of the patients observed were students at the Milwaukee Country Day School, where I was school physician, I could conveniently take specimens of blood during the periods of early incubation and of convalescence. Through the cooperation of interested physicians, it was possible for me to follow all these patients during their periods of quarantine as well. In addition, many cases were referred by colleagues for the sake of the study, and some were referred through the Milwaukee Health Department. It was often possible to extend the studies among siblings of the patients. Every one with the disease was confined to his own home; none was hospitalized. These conditions were highly valued, for they represented the true circumstances of chickenpox, which is universally treated in the home. There were no such complications in the series as erysipelas, cellulitis or encephalitis, nor in any case did the chickenpox follow another disease, as so often happens in hospitals during the course of an epidemic.

The control group consisted of those supposedly nonimmune contacts who had no rash. Some of them did not remain perfectly well, however, and the results of studies of their blood are particularly noted herein.

All smears were stained with Wright's stain, and Osgood and Ashworth's⁹ atlas was carefully followed. Every differential count was checked at least once, so that each recorded figure is based on a count of 200 cells.¹⁰

In all, 427 white cell counts and differential counts were done on 71 persons, 15 of whom were controls. On the series of 56 patients, 76 counts were made during incubation, 196 during the exanthema and 79 during convalescence. Seventy-six determinations were made on the control group. The data were collected in the course of the ten weeks beginning

7. Goldman, D.: Chickenpox with a Blood Picture Simulating That in Leukemia, *Am. J. Dis. Child.* **40**:1282-1284 (Dec.) 1930.

8. Holbrook, A. A.: The Coincidence of Chicken Pox and Lymphatic Leukemia: Report of a Case, *New England J. Med.* **216**:598-603 (April 8) 1937.

9. Osgood, E. E., and Ashworth, C. M.: *Atlas of Hematology*, San Francisco, J. W. Stacey, Inc., 1937.

10. Miss Patricia Johnston assisted me in the collection of specimens of blood for white cell counts and differential counts. Miss Gerda Meier assisted in the counting. Photomicrographs were taken by Dr. Stephen S. Stack.

Oct. 31, 1939 and ending Jan. 5, 1940. The charts (figs. 1-11) are constructed, however, in terms of the duration of the disease, a five week span.

Forty-four males and 27 females were studied. Students of Milwaukee Country Day School numbered 39; other persons, 32. The age distribution was as follows:

Age	No of Cases	Age	No. of Cases	Age	No of Cases
5 mo.	1	9 yr.	6	26 yr.	2
2 yr.	1	10 yr.	6	28 yr.	1
4 yr.	7	11 yr.	1	29 yr.	1
5 yr.	7	12 yr.	9	39 yr.	1
6 yr.	3	13 yr.	6	41 yr.	1
7 yr.	3	14 yr.	3	58 yr.	1
8 yr.	10	15 yr.	1		

Figure 1 represents every white cell count made in the 56 cases of chickenpox. A few specimens of blood were taken earlier than the eleventh day before the appearance of the rash and a few later than the eleventh day of convalescence. The counts made on these specimens are grouped under -11 and $+11$, respectively. The rest of the counts are recorded exactly according to their magnitude and to their time relation to the disease. The values for each day were averaged, so that a resultant curve could be drawn. It is apparent that the number of white cells tends to fall during the end of the incubation period, reaching a low point on the second and third days of the rash. Thereupon, the swing is promptly upward to the level characteristic of the early incubation period. The lowest count obtained was 2,900.

In figure 2 is recorded each neutrophilic polymorphonuclear cell count, and in figure 3, the percentage of such cells in each sample of blood. The curve in the former is interesting on comparison with the trend brought out in figure 1. The polymorphonuclear cell count falls, of course, with the white cell count, but its recovery is on a much more gradual gradient. On the other hand, the curve for the total lymphocyte count (fig. 4) descends as leukopenia develops but recovers far quicker than that for the polymorphonuclear cells. This phenomenon can be demonstrated in another way by comparing the percentages of polymorphonuclear neutrophils obtained in the differential count (fig. 3) with the total percentage of lymphocytes (fig. 5). Their resultant curves are shown together in figure 6. It is clear that the percentage of lymphocytes rises sharply from the second to the fifth day of the rash, and the percentage of polymorphonuclear leukocytes falls proportionally. Since the average white cell count is normal on the fifth day (8,650 per cubic millimeter) and the percentage of lymphocytes is high (59), one must conclude that at that time there is both a relative and an absolute lymphocytosis.

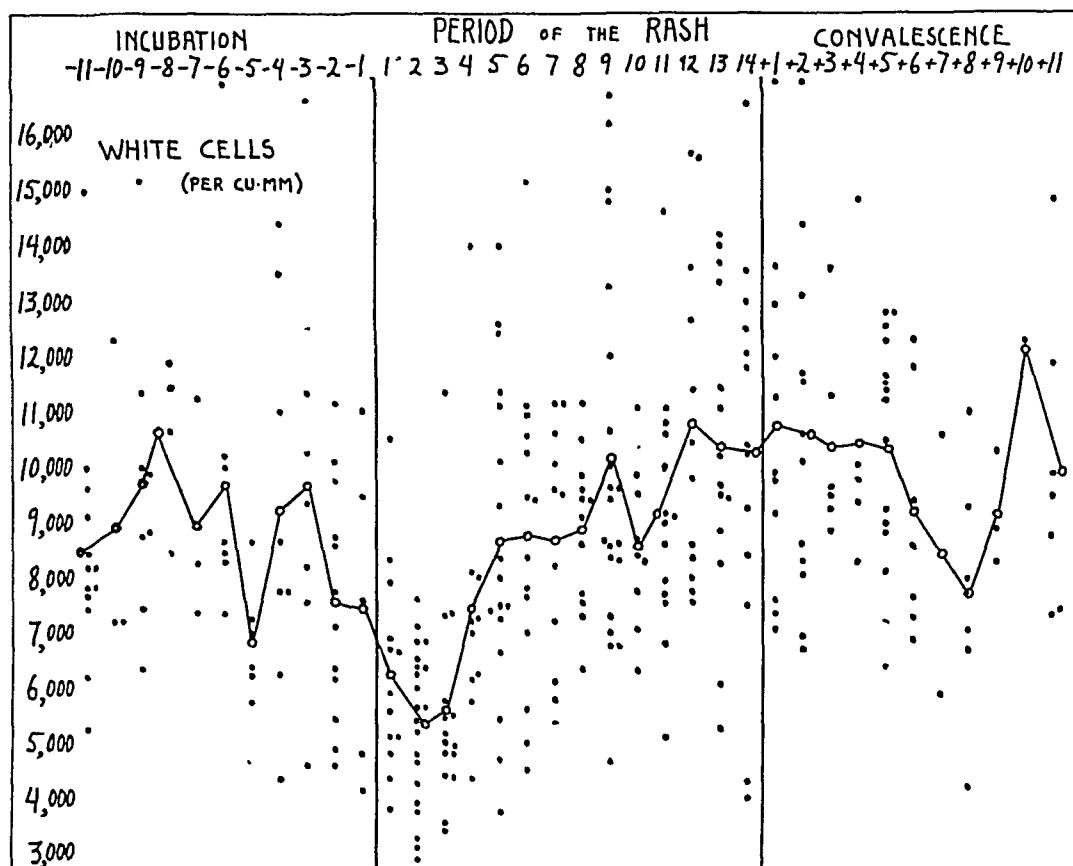


Fig. 1.—White cell counts in 56 cases of chickenpox.

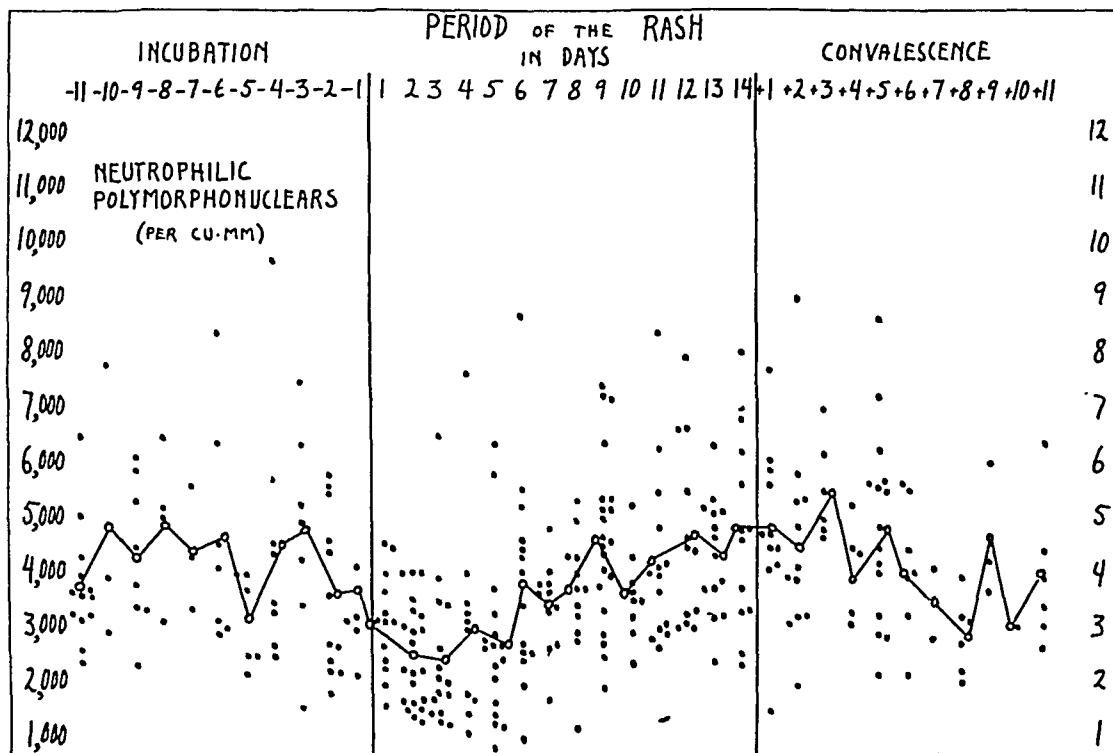


Fig. 2.—Counts of neutrophilic polymorphonuclear leukocytes in 56 cases of chickenpox.

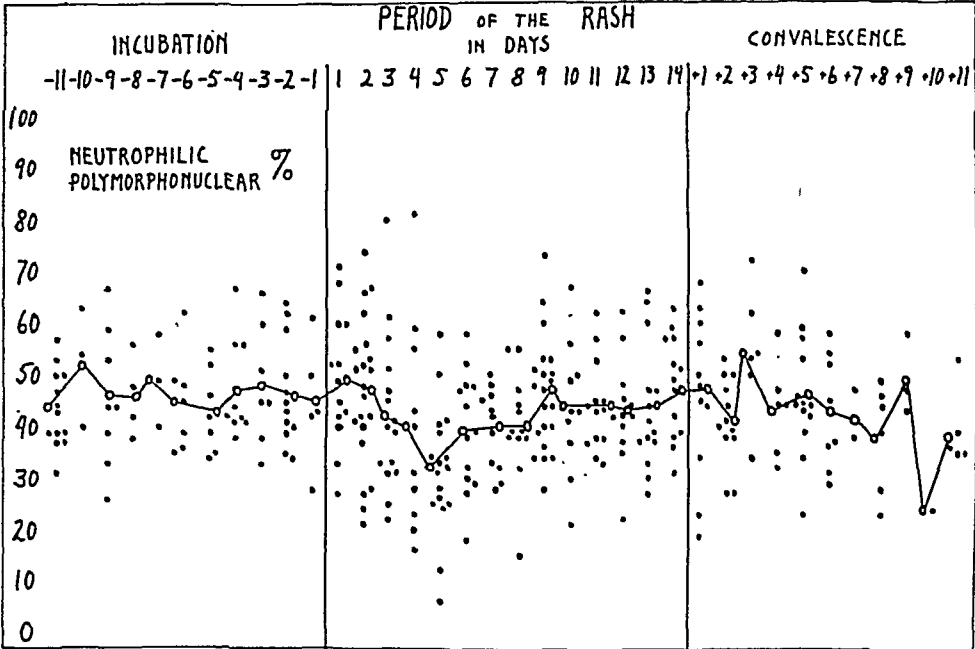


Fig. 3.—Percentage of neutrophilic polymorphonuclear leukocytes in 56 cases of chickenpox.

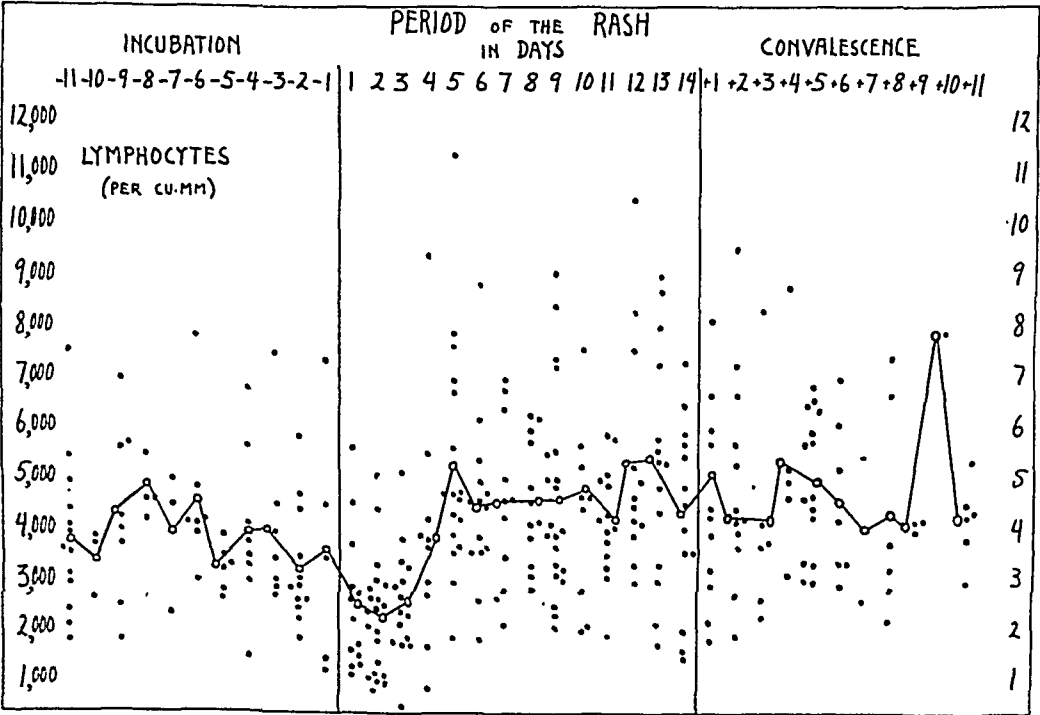


Fig. 4.—Lymphocyte counts in 56 cases of chickenpox.

As would be expected, young lymphocytes (fig. 7) do begin to appear in increasing numbers a day or two before the total lymphocyte count swings upward. The prolymphocytes attain marked prominence by the fifth day. Indeed, throughout the course of the rash both prolymphocytes

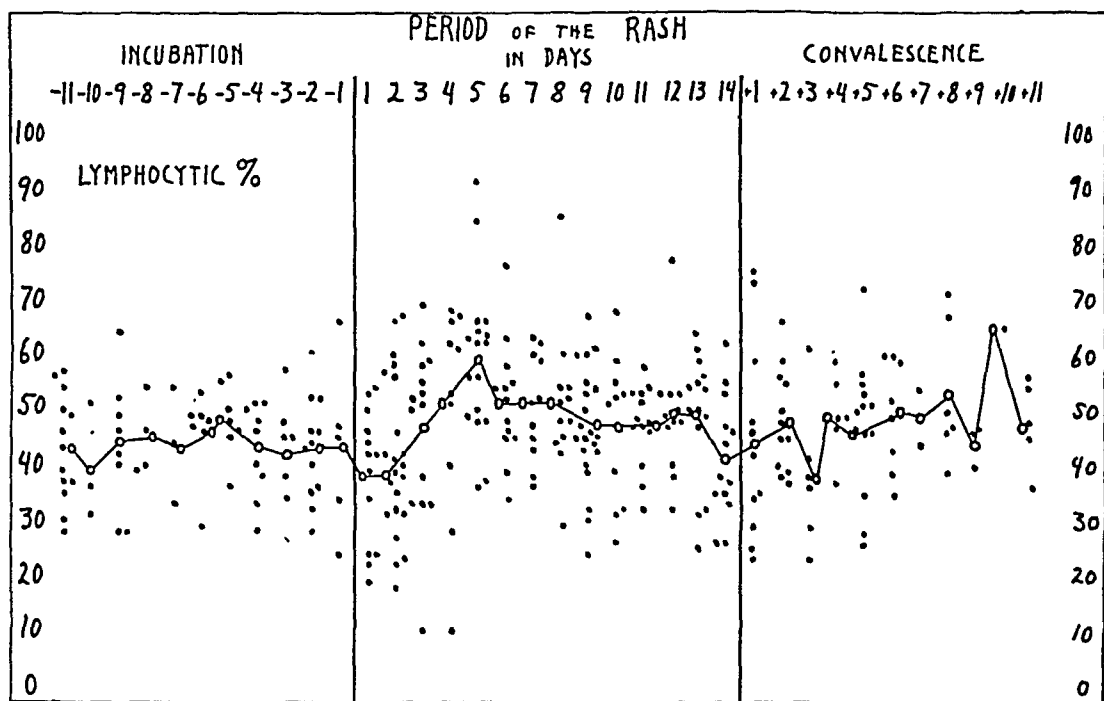


Fig. 5.—Percentage of lymphocytes in 56 cases of chickenpox.

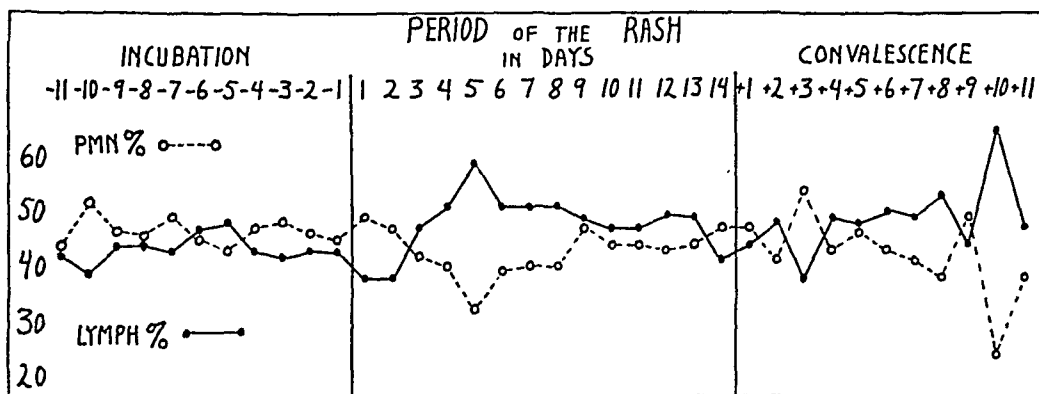


Fig. 6.—Comparison of percentages of neutrophilic polymorphonuclear leukocytes and lymphocytes in 56 cases of chickenpox.

and lymphoblasts are more conspicuous than during the incubation period.

Figure 8 shows the curve of the plasma cell counts, which is like the curve for prolymphocytes in figure 7. The plasma cells, however, reach their peak a day later.

The curve of the monocyte counts in figure 9 is just as indifferent as those for eosinophils and basophils would be, judging from the figures. No significant rise in eosinophils was observed before or during the period of convalescence.

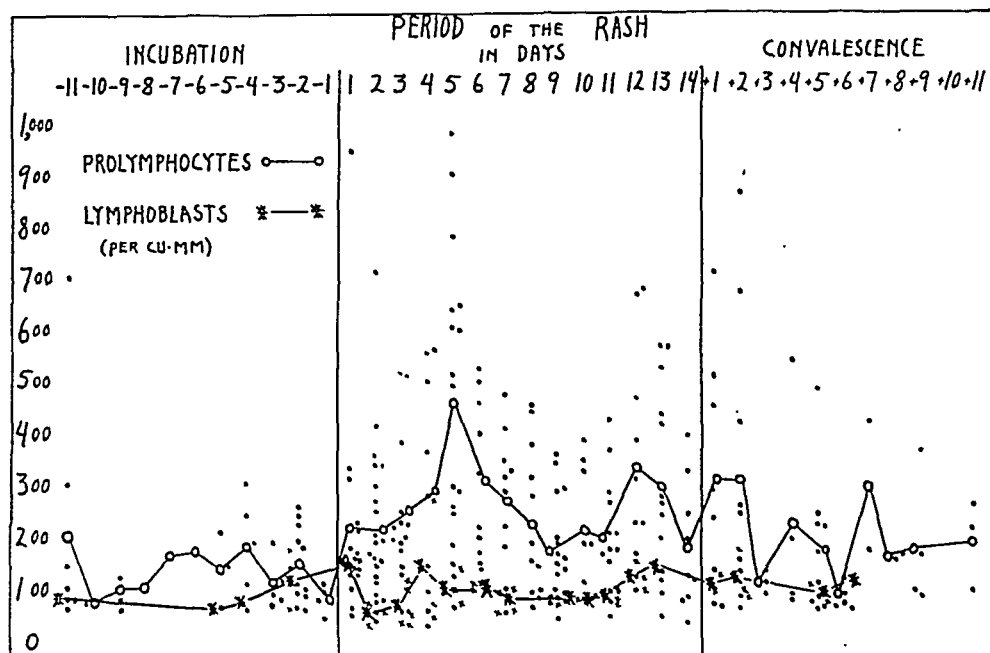


Fig. 7.—Counts of prolymphocytes and lymphoblasts in 56 cases of chickenpox.

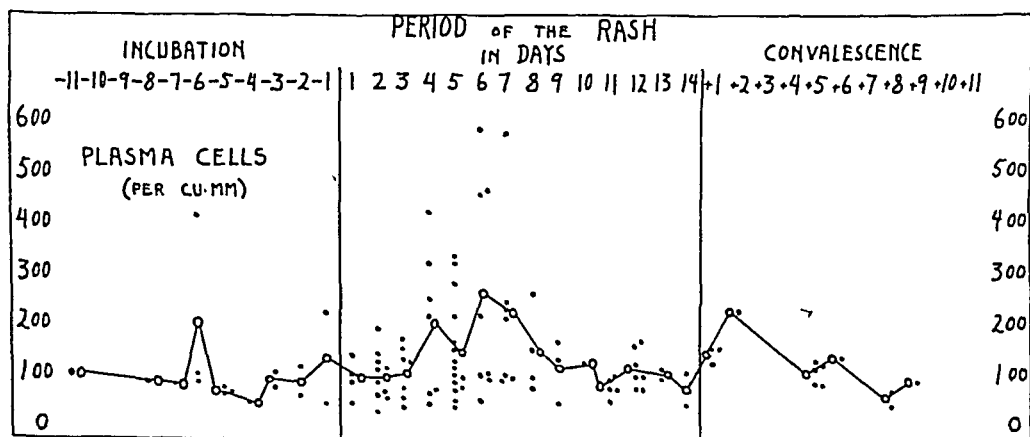


Fig. 8.—Counts of plasma cells in 56 cases of chickenpox.

Figure 10 gives a composite picture of the curves from figures 1, 2, 4, 7, 8 and 9. Thus, the significant blood counts, including some of their fractions, are summarized graphically.

Figure 11, which typifies the kind of graph obtained for the control group, is the only one presented here. The data represent the total

number of lymphocytes, a fact which makes this curve comparable to that in figure 4. The only tendency regularly appearing in the determinations which were made on the controls was toward a horizontal line.

During the incubation period in 16 cases of chickenpox, two or more determinations were made, of which the last came within three days of the breaking out of the rash. Thus, a basis for comparison existed, which furnished evidence in some instances that definite changes were occurring. In 5 cases there were an appreciable fall in the white cell

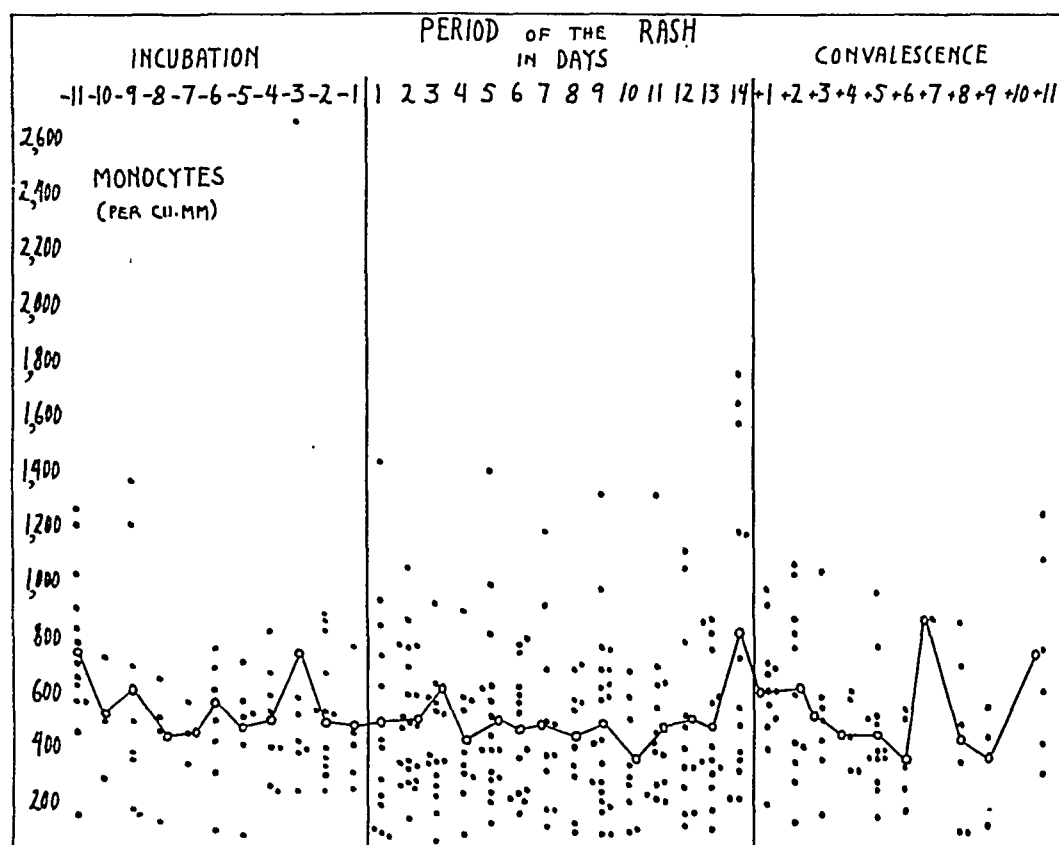


Fig. 9.—Counts of monocytes in 56 cases of chickenpox.

count to the neighborhood of 5,000 and a concomitant appearance of prolymphocytes to the extent of 2 to 4 per cent. In 4 other cases, besides a similar increase in immature lymphocytes, there was a fall in the percentage of polymorphonuclear leukocytes and a rise in the percentage of lymphocytes.

In the control group, similar surveys were possible in 14 of the 15 cases. The counts running up to the second day of the expected period of eruption were included. In only 1 instance did the white cell count fall to the region of 5,000. But prolymphocytes in percentages of 2 to 4 appeared in all 14 cases, and dislocation of the blood formula with a fall

in the percentage of polymorphonuclear leukocytes and a rise in the percentage of lymphocytes occurred eleven times.

From these observations one must conclude that no regular significant changes in the blood picture occur in the late incubation period of chickenpox to indicate that the rash is about to break out. However, it

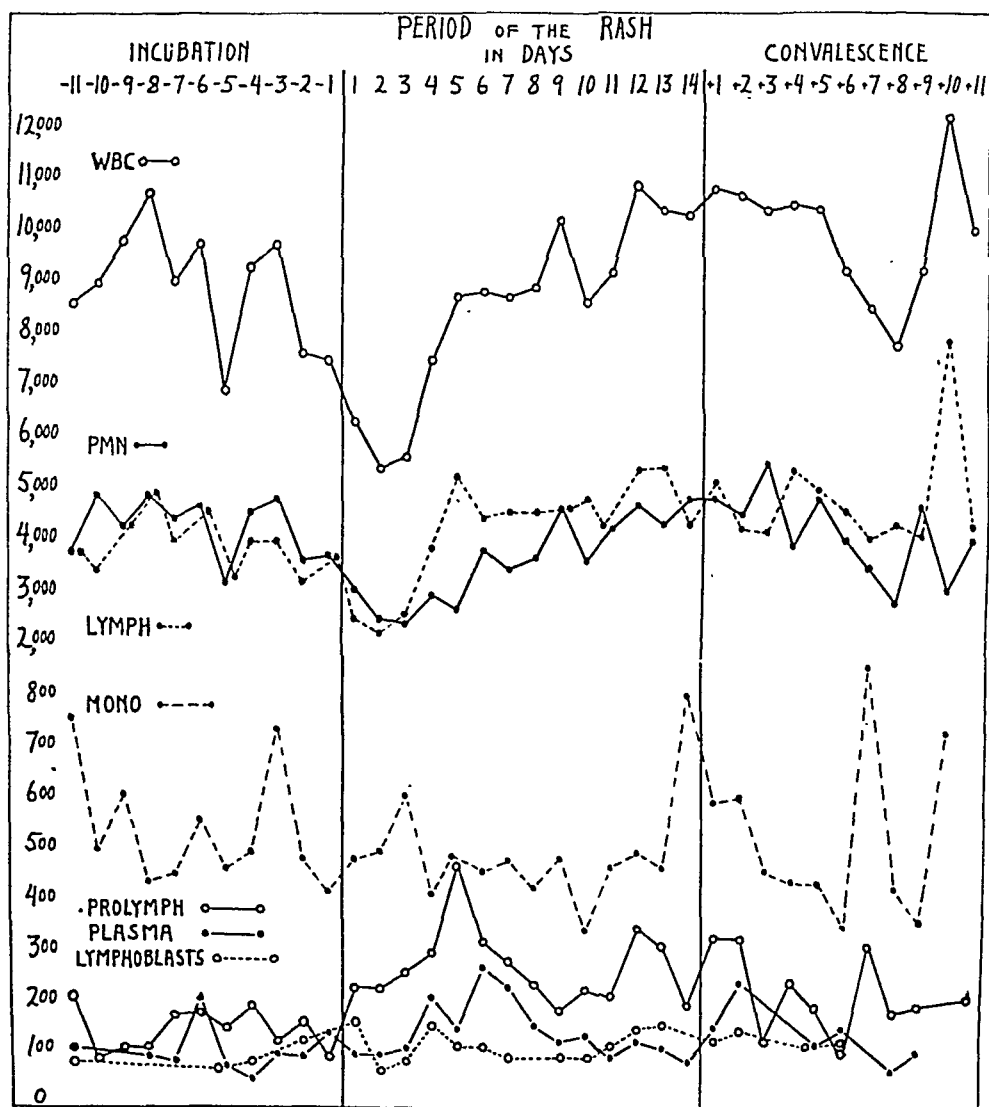


Fig. 10.—Comparison of counts of white cells, neutrophilic polymorphonuclear leukocytes, lymphocytes, monocytes, prolymphocytes, plasma cells and lymphoblasts in 56 cases of chickenpox.

is my impression that a fall in the white cell count to 5,000 per cubic millimeter or less, principally at the expense of the neutrophilic polymorphonuclear cells, combined with the appearance of immature lymphocytes, does definitely herald the eruption in the small number of cases in

which this combination occurs. As the figures show, these features characteristically do not become full blown until the second to the fifth day of the rash. Indeed, in some instances there may be a delay beyond that point; in others, a premature appearance.

The final distinguishing item in the blood formula of varicella is the plasmacytosis, which occurred in 50 per cent of the cases. The range of percentages of plasma cells in these differential counts was 2 to 8. Since appreciable numbers of plasma cells are known to occur in only a few conditions, such as multiple myeloma, plasmacytic leukemia, German measles and measles, it was surprising to encounter 2 patients in the control group of 15 who showed counts higher than 2 per cent. Results

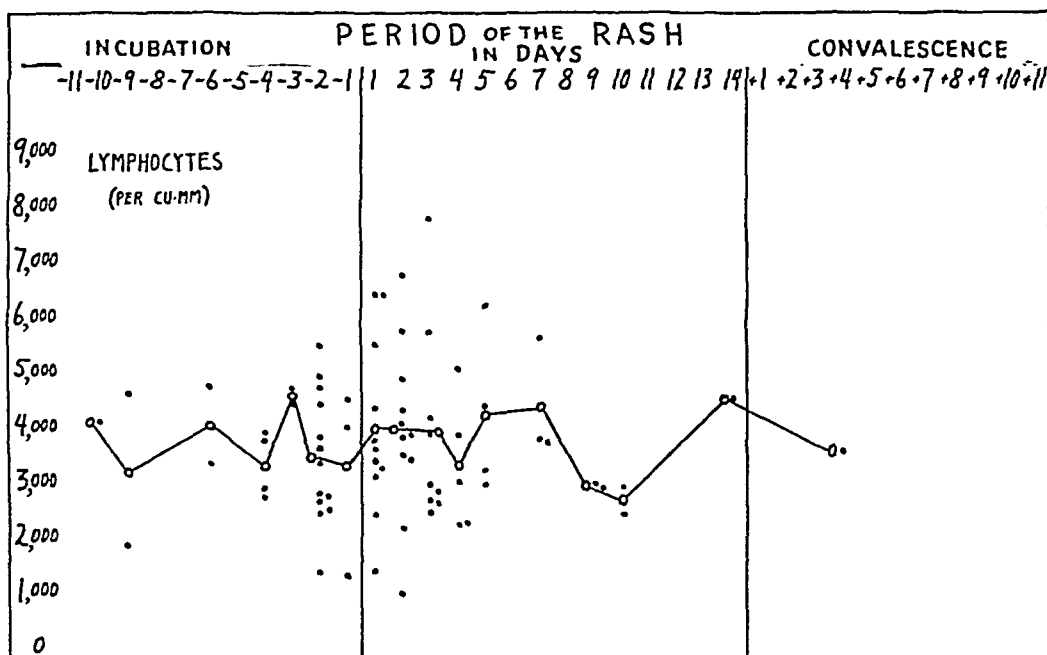


Fig. 11.—Lymphocyte counts for a control group of 15 supposedly nonimmune contacts in whom no visible evidences of chickenpox appeared.

of studies of their blood are given in the table (cases 1 and 2). The first was a boy of 13 who was exposed to chickenpox on Nov. 9, 1939. On the third day of the period when his rash was expected to develop, the percentage of plasmacytes was 7. At the same time the percentage of polymorphonuclear cells was falling and the percentage of lymphocytes was rising, with immature cells present. There was, however, no leukopenia. Nevertheless, the boy felt sick and suffered from the usual symptoms of a mild infection of the upper respiratory tract. The most likely explanation for this condition is that the patient had an abortive form of chickenpox, with the exanthema lacking.

The second control patient (table, case 2) was a 4 year old girl in whom plasmacytes were prominent two days before the rash was due.

Results of Studies of the Blood of Three Controls and Four Patients with Chickenpox

Case No.; Sex; Age and Classification of Subject	Date	Day of Disease *	Polymorphonuclear Leukocytes					Lymphocytes				Plasmacytes				Monocytes			Eosinophils, Percentage	Basophils, Percentage
			Segmented Cells, Percentage	Band Cells, Percentage	All Cells, Total Percentage	Number of Cells	Mature Cells, Percentage	Prolymphocytes, Percentage	Lymphoblasts, Percentage	All Cells, Percentage	Number of Cells	Mature Cells, Percentage	Plasmablasts, Percentage	All Cells, Percentage	Number of Cells	Monocytes, Percentage	Promonocytes, Percentage	Number of Cells		
1 M, 13 Control	11/13	-10	55	1	56	5,795	39	39	4,017	3	..	369	1	1
	11/17	-6	54	2	56	8,456	26	9	..	31	4,631	11	..	1,661	1	1
	11/21	-1	62	..	62	8,122	17	4	..	21	2,761	14	3	1,661	1	1
	11/25	3	39	8	47	5,264	27	5	2	34	3,808	7	..	7	784	8	..	896	8	..
	11/29	7	38	1	39	4,816	41	4	..	45	5,557	2	..	2	247	13	..	1,599	1	..
2 F, 4 Control	12/3	-2	44	..	44	4,884	45	2	2	49	5,439	3	..	3	333	4	..	444
	12/5	1	51	..	51	3,978	36	6	1	43	3,854	1	..	1	78	1	..	78
	12/7	3	32	..	32	4,320	57	57	7,695	1	..	1	135	10	..	1,350
	12/5	-4	52	..	52	4,880	39	2	..	41	3,854	7	..	668
	12/7	-2	30	..	30	1,815	58	3	1	62	3,751	6	1	363	1	..
3 M, 13 Control	12/9	1	43	1	43	5,590	48	1	..	49	6,370	3	..	390	5	..
	12/10	2	42	1	43	4,294	48	48	3,840	8	..	704	1	..
	12/11	3	59	..	59	4,926	33	33	2,755	1	..	1	83	5	..	417	2	..
	11/13	-9	25	..	26	2,288	53	1	..	64	5,632	4	..	352	5	1
	11/16	-6	39	..	39	2,866	53	53	3,895	4	..	294	4	..
4 M, 8 Chickenpox	11/18	-4	40	1	41	4,510	50	1	..	53	5,610	6	..	660	2	..
	11/20	-2	49	1	50	3,550	34	2	..	36	2,556	11	1	852	1	..
	11/22	1	36	4	40	1,520	36	4	4	44	1,672	9	2	76	1	..
	11/25	4	18	2	20	1,600	57	7	4	68	5,440	4	..	4	320	4	..	320	3	1
	12/1	10	34	..	30	2,850	57	2	..	59	5,605	6	..	570	4	1
5 F, 13 Chickenpox	12/4	14	30	2	36	3,690	51	4	..	55	5,637	7	..	714	2	..
	12/8	+4	35	..	35	5,197	56	3	..	59	8,761	2	..	296	3	1
	12/5	-3	33	..	33	1,518	55	2	..	57	2,644	5	..	230	4	1
	12/7	-1	61	..	61	2,928	23	1	..	24	1,152	9	..	402	4	1
	12/8	1	70	1	71	3,940	16	3	..	19	1,054	6	1	385	3	..
6 F, 41 Chickenpox	12/9	2	50	5	55	2,145	29	2	..	31	1,009	12	..	468	1	1
	12/12	5	25	..	25	1,177	51	11	..	62	2,914	1	..	1	47	3	1	188	5	3
	12/15	8	39	..	39	3,685	50	1	..	51	4,819	3	..	283	6	1
	12/18	11	44	..	44	3,960	44	2	..	46	4,140	4	..	360	5	1
	12/21	14	49	..	49	4,532	37	1	..	38	3,515	4	..	370	8	1
7 M, 12 Chickenpox	11/21	2	66	1	67	2,177	17	5	1	23	747	10	..	325
	11/24	5	26	2	28	2,030	54	9	..	63	4,567	1	..	3	216	6	..	435
	11/25	6	28	4	32	2,480	48	6	..	54	4,185	6	..	6	462	5	2	155	..	1
	11/28	9	73	..	73	6,314	24	24	2,076	2	..	173	1	..
	12/1	12	57	..	57	4,389	35	3	..	38	2,926	1	..	1	77	2	..	154	..	2
8 M, 12 Chickenpox	12/8	+5	70	..	70	8,060	24	1	1	26	2,990	3	..	345	1	..
	11/17	-18	39	..	39	3,207	43	43	3,526	10	..	820	8	..
	11/21	-14	57	..	57	3,534	27	1	..	28	1,736	13	..	630	5	..
	11/23	-12	53	..	53	4,270	29	1	..	30	2,355	10	..	1,020	4	..
	12/5	1	58	2	60	3,090	23	1	..	24	1,236	16	..	834
9 M, 12 Chickenpox	12/6	2	40	1	41	1,180	34	3	..	37	1,073	..	1	1	29	16	..	464	4	1
	12/11	7	50	..	50	3,600	32	4	..	36	2,692	8	..	8	576	5	..	360	1	..
	12/15	11	51	2	53	2,703	35	1	..	36	1,836	1	..	1	51	5	..	255	3	2
	12/20	+2	44	1	45	3,015	39	1	..	40	2,680	10	..	670	5	..

* A figure preceded by a minus sign signifies the number of days before the rash appeared, while a figure preceded by a plus sign signifies the number of days of convalescence.

Then, as in case 1, the polymorphonuclear cell count fell and the lymphocytes increased, with young forms appearing. Though she was apparently as well as usual during the period when a rash was expected to develop, I can account for the blood changes only on the basis of reaction to the chickenpox virus.

Another control was a boy of 13, whose counts are presented in the table (case 3). In view of the changes occurring on Dec. 7, 1939 I believed the rash was going to develop. But this did not happen. I can only interpret the data as I have in the 2 previous instances.

The table (case 4) also gives the figures obtained on a boy of 8, whose eruption appeared on Nov. 22, 1939. The low white cell count of 3,800, the fall in percentage of polymorphonuclear leukocytes to 20, the rise in percentage of lymphocytes to 68, with prolymphocytes and lymphoblasts in prominence, and the appearance of plasmacytes all made the picture

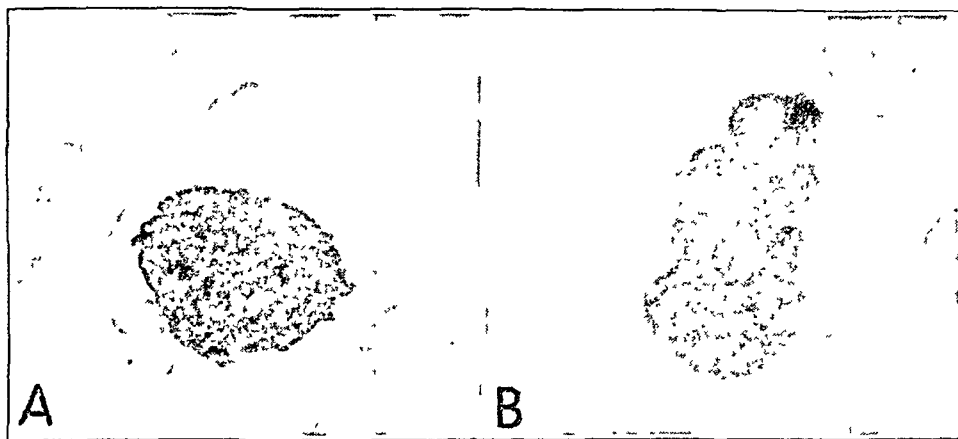


Fig. 12.—Prolymphocytes from smears of blood taken from patients with chickenpox. *A*, cell in prophase stage of mitotic division, and *B*, cell probably undergoing mitotic division.

typical. The data in the table (cases 5, 6 and 7) also indicate the usual findings in cases of chickenpox and represent, respectively, the cases of a girl of 13, a woman of 41 and a boy of 12.

Emphasis has repeatedly been placed on the fact that immature lymphocytes enter the blood picture of varicella, especially during the early period of the rash. Not only are lymphoblasts frequently encountered, but in addition one occasionally notes prolymphocytes undergoing mitotic division. Examples of the latter cells, so unusual in peripheral blood, are shown in figure 12.

In view of this evidence for powerful stimulus to lymphocytic activity in chickenpox, one cannot be surprised on occasion to see leukemoid reactions in this disease. Furthermore, these observations make the association between chickenpox and lymphatic leukemia, alluded to in an introductory paragraph, seem somewhat less "coincidental." Possibly

the effects of the virus are more causal than casual in the pathogenesis of the malignant condition. Recent articles in the literature are pertinent. Furth¹¹ has said, "It is remarkable that a virus can be found in associa-

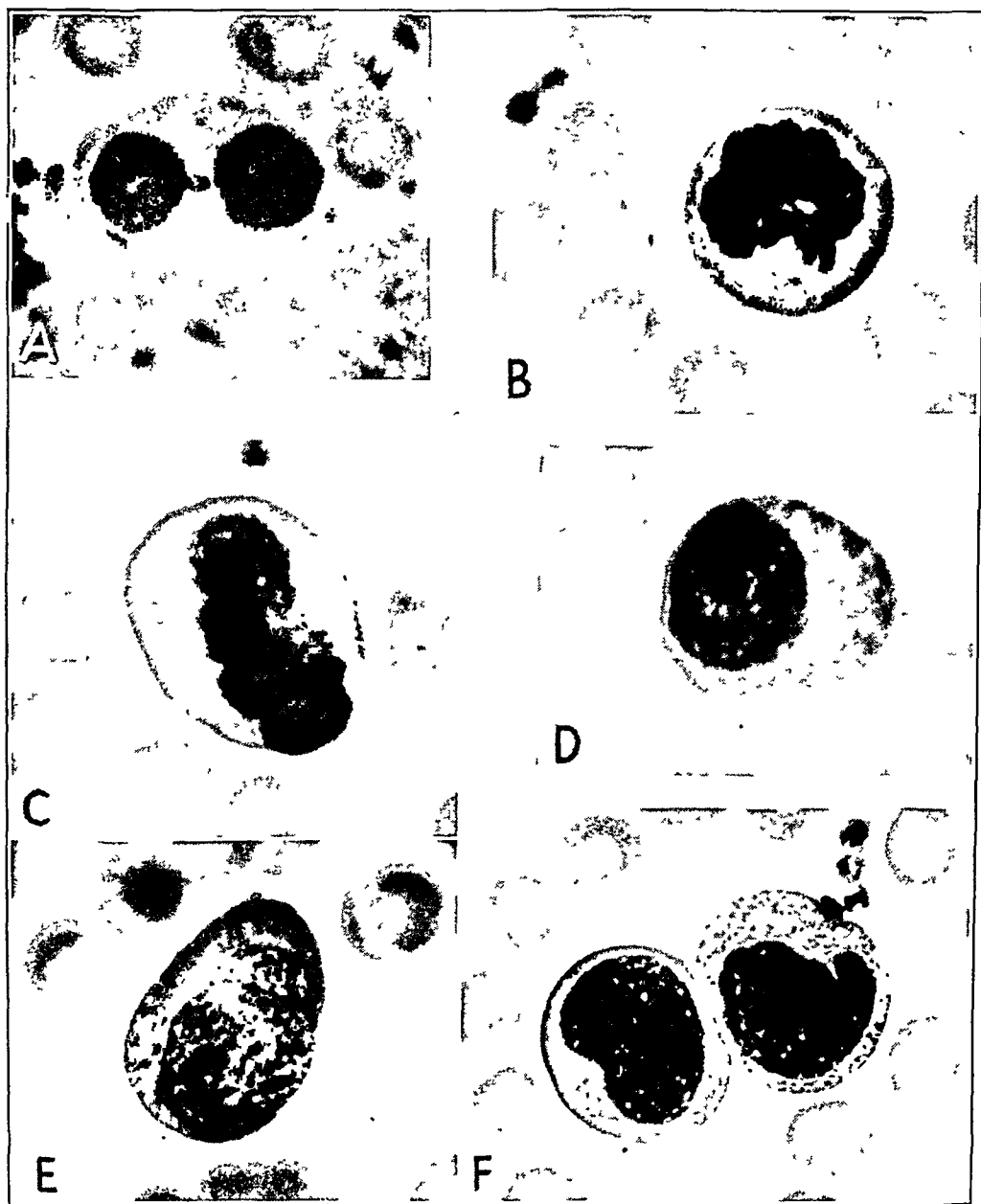


Fig. 13.—Plasmacytic and lymphocytic forms found in routine differential counts made on blood taken from patients with chickenpox. *A*, plasmacyte with two nuclei (amitotic division); *B*, proplasmacyte in early metaphase stage of mitosis; *C*, proplasmacyte with a long nucleus; *D*, typical plasmacyte; *E*, plasma-blast, and *F*, lymphoblast and monocyte for comparison.

11. Furth, J., in Symposium on Blood and Blood-Forming Organs, Madison, Wis., The University of Wisconsin Press, 1939.

tion with almost all the strains of leukosis and sarcoma of birds that are readily transmissible." Gerundo¹² has written, "The virus theory of the leukemias should receive more attention." Taylor¹³ quoted Andrewes as follows: "There is no proof yet that a virus is concerned in the etiology of cancer in general. But there is evidence to make that idea worth very careful attention." Since the chickenpox virus has not yet been identified and cultivated, there is no animal experimentation along the lines just suggested.

Figure 13 includes interesting plasma cells found in smears of blood from patients with chickenpox. This disease offers an excellent opportunity indeed for studying this type of cell.

SUMMARY

This study was made during an epidemic of chickenpox in Milwaukee County in the fall of 1939. The 56 patients and 15 controls were all quarantined in their homes. White cell counts and differential counts, done serially on each person, are presented graphically.

The following significant tendencies are noted in the patients:

1. The total white cell count falls during the end of the incubation period, reaches the lowest level on the second and third days of the rash and then rises to its former level.
2. During the leukopenia, the percentage of polymorphonuclear cells falls and the percentage of lymphocytes rises, as lymphoblasts and prolymphocytes come into prominence. Among the latter, the mitotic figures which are occasionally seen attest further to the strong stimulus to lymphocytic activity which apparently accompanies chickenpox.
3. An increase in plasma cells is also noteworthy early in the eruption stage, their portion of the total differential count sometimes reaching 6 to 8 per cent.
4. In some instances, several of the foregoing features may appear before the rash and thus may be of diagnostic value.

The studies on the control group show the following tendencies:

1. In the aggregate, the various plotted curves for total white blood cell counts and their fractions tend toward a horizontal line.
2. In certain individual cases, a fall in the percentage of polymorphonuclear cells and a rise in the percentage of lymphocytes, with prolymphocytes increasing, occur at about the time the eruption is expected.

12. Gerundo, M.: Acute Leukemia and Erythremia, *J. Kansas M. Soc.* **40**: 460-462 (Nov.) 1939.

13. Taylor, G. W.: Cancer, *New England J. Med.* **221**:779-783 (Nov. 16) 1939.

CONCLUSIONS

1. A drop in the total white blood cell count to 5,000 per cubic millimeter or less, principally at the expense of the neutrophilic polymorphonuclear cells, combined with the appearance of immature lymphocytes and plasma cells constitutes the significant feature in the moving blood picture of chickenpox. When this combination is noted in the incubation period, the onset of the rash may be prophesied with fair accuracy.

2. Sometimes when such forecasts are wrong, one may be dealing with cases of the abortive form.

3. There is a striking lymphocytic reaction in chickenpox, which in susceptible persons may be decisive in producing lymphatic leukemia.

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HEPATIC FUNCTION IN PATIENTS WITH AMYLOIDOSIS

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The marked pathologic changes that occur when the liver is infiltrated with amyloid make functional studies of such an organ of more than academic interest. The paucity of reports in the literature is due to the uncertainty in clinical diagnosis and to the comparative lack of material, since in general hospitals amyloidosis is infrequently seen. We have attempted to surmount these difficulties by using the improved congo red absorption test¹ to confirm the diagnosis and by conducting our studies at a large hospital for tuberculous patients (Sea View).

SOURCE OF MATERIAL

Patients who showed 100 per cent absorption of congo red dye from the blood stream at the end of one-half hour after the intravenous injection of 10 cc. were chosen for this study. Most patients presented albuminuria and cylindruria of varying degree, and a significant number had enlarged palpable livers and tuberculous enterocolitis. The presence of an enlarged liver in these patients was considered evidence of amyloid infiltration, although the absence of hepatomegaly does not rule out the possibility of amyloid being present. Persistent complaints of abdominal symptoms in the presence of pulmonary tuberculosis were considered evidence for tuberculous enterocolitis. The degree of severity of constitutional symptoms was arbitrarily based on the presence of cough, expectoration, night sweats, appetite, loss of weight and elevations of temperature (table 1).

As many as possible of the following indexes of hepatic function were determined for each patient: icterus index, bromsulphalein absorption, galactose tolerance, urinary urobilinogen excretion, Takata-Ara reaction, serum proteins, dextrose tolerance and blood constants.

From the Metabolic Service of Sea View Hospital.

1. Tiber, A. M.: Improved Congo Red Test, to be published.

TABLE 1.—Summary of Clinical Condition and Reactions to Tests of Hepatic Function

Case No.	Tuberculosis		State of Nutrition	Temperature	Liver Palpable	Edema Present	Congo Red Retention, Percentage	Urinary Albumin Excretion	Urinary Urobilinogen Excretion	Icterus Index	Bromsulphalein Retention	Galactose Excretion	Dextrose Tolerance
	Lung	Intestine											
1	Advanced	+	Poor	Septic	+	+	100	+	...	4.0	Trace	Prolonged
2	Advanced	+	Poor	Septic	+	0	100	+	1:5	4.0	None	1.1	Prolonged
3	Advanced	+	Fair	Normal	+	0	100	+	1:1	4.0	None	0	Prolonged
4	Advanced	+	Poor	Septic	+	+	100	+	...	4.5	Trace	Prolonged
5	Advanced	+	Poor	Normal	+	+	100	+	1:5	4.5	5%	0	Prolonged
6	Advanced	0	Fair	Normal	+	0	100	+	1:1	4.5	None	1.7	Prolonged
7	Advanced	0	Good	Normal	0	0	100	0	1:1	...	Trace	0.25	Prolonged
8	Advanced	0	Good	Normal	0	0	100	0	1:1	0	Prolonged
9	Moderate to advanced	0	Fair	Normal	0	0	100	0	1:1	0.75	Normal
10	Advanced	0	Good	Normal	+	0	100	+	1:1	...	5%	0	Prolonged
11	Advanced	0	Fair	Normal	+	0	100	+	1:1	4.0	Trace	3.3; 1.1	Normal
12	Advanced	0	Poor	Normal	+	0	100	+	...	4.0	0	Normal
13	Advanced	0	Good	Normal	+	0	100	+	1:1	5.0	0	Normal
14	Advanced	0	Fair	Normal	+	0	100	+	1:1	...	None	1.2	Prolonged
15	Advanced	+	Poor	Septic	+	+	100	+	...	3.5	None	Normal
16	Advanced	0	Good	Normal	+	0	100	+	1:1	4.5	Trace	0.6	Normal
17	Advanced	+	Poor	Normal	+	0	100	+	1:1	4.0	1.0
18	Advanced	+	Poor	Septic	+	0	100	0	1:10	1.1
19	Advanced	0	Poor	Septic	0	0	100	0	1:1	0.3

ICTERUS INDEX

Approximately 30 patients with amyloidosis have been observed in the wards for a period of three months to a year, and in no case have we seen clinical jaundice develop. By the Meulengracht² technic, the icterus index for 12 patients studied was found to be within normal limits, that is, less than 6 (table 1).

A review of the clinical records of 100 patients with amyloidosis on whom autopsy was performed revealed in only 1 case clinical jaundice of short duration and of acute onset. These findings are consistent with the observations of others that the incidence of icterus in amyloidosis is low.

BROMSULPHALEIN ABSORPTION

The bromsulphalein test, introduced in 1925 by Rosenthal and White,³ has been generally accepted as the most satisfactory test of liver function in the absence of jaundice. Using a dose of 2 mg. of the dye per kilogram of body weight and taking specimens of blood at the end of five and of thirty minute periods, they found that in 30 normal controls none or only a trace of dye remained in the blood stream at the end of the half-hour period. MacDonald⁴ showed that there is a definite curve of disappearance of the dye and that in 23 of 25 normal persons studied all of the dye had disappeared in eighteen minutes.

Retention of the dye has been reported⁵ to occur in patients with such diversified diseases of the liver as cirrhosis, chronic atrophy, Banti's syndrome, hemochromatosis, chronic passive congestion, Pick-Concato disease, extensive fatty degeneration, amyloidosis and toxic or infectious hepatitis and in the recovery state of hepatogenous jaundice. Bauman and Orr⁶ reported dye retention to be consistently associated with histologic evidence of damage to the liver.

This excretory function of the liver was determined for 12 patients. The technic described by Rosenthal and White³ was used. In 5 instances the removal of the dye was complete at the end of the half-hour. In 5 a trace remained, and in 2 there was 5 per cent retention

2. Meulengracht, E.: Die klinische Bedeutung der Untersuchung auf Gallenfarbstoff in Blutserum, *Deutsches Arch. f. klin. Med.* **132**:285-300, 1920.

3. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84**:1112-1114 (April 11) 1925.

4. MacDonald, D.: Bromsulphalein Test, *Canad. M. A. J.* **39**:556-560 (Dec.) 1938.

5. Snell, A. M., and Magath, T. B.: The Use and Interpretation of Tests for Liver Function: A Clinical Review, *J. A. M. A.* **110**:167-174 (Jan. 15) 1938.

6. Bauman, L., and Orr, L.: Bromsulphalein Test Checked with Liver Histology, *New York State J. Med.* **38**:1161 (Sept. 1) 1938.

at the end of a half-hour (table 1). Weir⁷ has pointed out that in the absence of jaundice even slight retention of the dye (4 per cent) is significant and that the degree of retention parallels the degree of hepatic involvement. According to these criteria, it must be concluded that there was a minor degree of hepatic dysfunction in 2 of the 12 patients studied. Both of them had hepatomegaly.

GALACTOSE TOLERANCE

A normal person can assimilate an oral dose of 40 Gm. of galactose without excreting in the urine more than 3 Gm. in the ensuing four to five hours. This rate has been shown to be independent of age, sex or weight. The excretion of more than 3 Gm. in five hours is said to denote damage to the parenchyma of the liver.⁸ However, Banks and his co-workers⁹ have pointed out that the reaction to this test is consistently negative in cases of biliary and portal cirrhosis, and Snell and Magath⁵ stated that it has "no value whatever in cases in which the patients are not visibly jaundiced."

In 17 determinations the galactose tolerance of 16 patients with amyloidosis was entirely within normal limits. As extensive damage to the parenchyma is necessary before there is sufficient derangement of galactose metabolism to yield an abnormal result, these findings are congruous with the essentially normal icterus index and bromsulphalein retention values.

URINARY EXCRETION OF UROBILINOGEN

Through the action of bacteria, bile pigment in the intestine is transformed into urobilin, urobilinogen and stercobilin. Normally, a portion of the urobilinogen is absorbed and resynthesized by the liver and only a small amount is excreted in the urine. If the parenchyma of the liver is even slightly damaged¹⁰ increased amounts of urobilinogen appear

7. Weir, J. F.: Hepatitis: Some Forms Not Commonly Recognized, *J. A. M. A.* **111**:1356-1362 (Oct. 8) 1938.

8. Bauer, R.: Unsere Kenntnisse über Leberfunktion und ihre Verwertung für die Klinik, *Wien. klin. Wchnschr.* **45**:1577-1581 (Dec. 23) 1932. Shay, H., and Schloss, E.: Painless Jaundice: Its Differential Diagnosis by the Galactose Tolerance Test, *J. A. M. A.* **98**:1433-1436 (April 23) 1932. Shay, H.; Schloss, E. M., and Bell, M. A.: Metabolism of Galactose, *Arch. Int. Med.* **47**:391-402 (March) 1931.

9. Banks, B. M.; Sprague, P. H., and Snell, A. M.: Clinical Evaluation of the Galactose Tolerance Test, *J. A. M. A.* **100**:1987-1993 (June 24) 1933.

10. (a) Watson, C. J.: Studies in Urobilinogen: Urobilinogen in Urine and Feces of Subjects Without Evidence of Disease of Liver or Biliary Tract, *Arch. Int. Med.* **59**:196-231 (Feb.) 1937. (b) Sparkman, R.: Studies in Urobilinogen: Simple and Rapid Method for Quantitative Determination of Urobilinogen in Single Specimens of Urine and Stool, *ibid.* **63**:858-883 (May) 1939.

in the urine. When bile is absent from the intestinal tract, no urobilinogen is excreted, though the damage to the liver may be extensive. Because on exposure to the air urobilinogen is oxidized to urobilin, some workers⁵ convert urobilinogen into urobilin and then determine the amount of the latter. The use of fresh specimens of urine obviate the necessity for this procedure. Wallace and Diamond¹¹ have shown that in dilutions up to 1:20 normal urine may give a positive reaction for urobilinogen. A positive reaction in higher dilution is considered definite evidence of damage to the liver.

Fresh specimens of urine from 15 patients with amyloidosis were repeatedly examined by the Wallace-Diamond method with Ehrlich's reagent (paradimethylaminobenzene), and in no case was the reaction positive in a dilution greater than 1:10 (table 1). These results are consistent with the type of pathologic changes found in amyloidosis of the liver, as the urinary excretion of urobilinogen is strikingly increased in acute rather than in chronic degenerative diseases of the liver. When in the latter diseases excretion of urobilinogen is affected, the increase is slight.¹²

BLOOD SERUM PROTEINS

Although there is difference of opinion¹³ as to the role of the liver in the production of the serum protein fractions, most investigators agree that in chronic diffuse parenchymatous disease of the liver the total proteins are reduced because of the lowering of the albumin fraction.¹⁴ Because the purpose of this study was to obtain data from patients with amyloidosis, we were obliged to use tuberculous persons.

11. Wallace, G. B., and Diamond, J. S.: Significance of Urobilinogen in the Urine as a Test of Liver Function and a Simple Quantitative Method, *Arch. Int. Med.* **35**:698-725 (June) 1925.

12. Rosenberg, D. H.: Galactose and Urobilinogen Tests in the Differential Diagnosis of Obstructive and Hepatic Jaundice, *Ann. Int. Med.* **8**:60-69 (July) 1934. White, F. W.: Galactose Tolerance and Urobilinogen in Differential Diagnosis of Painless Jaundice, *Am. J. Digest. Dis. & Nutrition* **4**:315-325 (July) 1937. Watson.^{10a}

13. (a) Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Proteins: II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion, *Am. J. Physiol.* **47**:370-378 (Dec.) 1918; III. Liver Injury Alone: Liver Injury and Plasma Depletion: The Eck Fistula Combined with Plasma Depletion, *ibid.* **47**:379-392 (Dec.) 1918. (b) Hulman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Given by Vein Utilized in Body Metabolism: II. A Dynamic Equilibrium Between Plasma and Tissue Proteins, *J. Exper. Med.* **59**:269-282 (March) 1934. (c) Peters, J. P., and Eisenman, A. J.: The Serum Proteins in Disease Not Primarily Affecting the Cardio-Vascular System or Kidneys, *Am. J. M. Sc.* **186**:808-833 (Dec.) 1933.

14. Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch. Int. Med.* **55**:349-359 (March) 1935. Snell and Magath.⁵

Since tuberculosis¹⁵ per se may cause an increase in the concentration of globulin, the blood serum protein fractions were determined for 30 patients with chronic tuberculosis but without amyloidosis, in order to find the range of values in persons with this disease at our institution. These findings (table 2) are at slight variance from those reported in the literature. The total protein concentration was normal (6.0 to 7.2 Gm. per hundred cubic centimeters); the globulin levels were in the upper normal range (2.0 to 2.7 Gm. per hundred cubic centimeters), while the albumin levels were slightly reduced (3.5 to 5.1 Gm. per hundred cubic centimeters). The average albumin concentration was 4.2 Gm. per hundred cubic centimeters.

Repeated determinations of blood serum proteins were carried out on 31 patients with chronic pulmonary tuberculosis and clinically proved

TABLE 2.—*Range of Values for Serum Proteins in Cases of Chronic Pulmonary Tuberculosis*

	Author's Series, Cases	Total Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.
No fluid in chest, no edema and no ascites....	11	6.3 - 7.1	3.7 - 4.8	2.2 - 2.7
Fluid in chest.....	7	6.0 - 7.2	3.7 - 5.1	2.0 - 2.5
Suppuration of bone.....	12	6.2 - 7.1	3.5 - 5.0	2.0 - 2.5
Total.....	30	6.0 - 7.2	3.5 - 5.1	2.0 - 2.7
Eichelberger and McCluskey's series.....		7.8 - 8.4	4.2 - 4.7	2.6 - 3.6
Range for normal persons.....		6.0 - 8.0	4.0 - 6.0	1.4 - 3.0

amyloidosis, as indicated in table 3. The total protein levels ranged from 5.0 to 8.0 Gm. per hundred cubic centimeters, the albumin from 2.4 to 4.8 Gm. and the globulin from 1.7 to 4.6 Gm. The average albumin concentration was 3.6 Gm. per hundred cubic centimeters. A further analysis of these data reveals that in 10 cases the total serum protein concentration was below 6 Gm. per hundred cubic centimeters and in 18 there was a significant reduction in the albumin fraction, to below 3.5 Gm. In 7 of the latter group the diagnosis of amyloidosis was clinically established prior to the onset of albuminuria, and thus an opportunity was afforded us to study the serum protein partition in the absence of proteinuria. Table 4 shows that the total protein levels in these cases ranged from 6 to 7 Gm. per hundred cubic centimeters, the albumin from 2.4 to 4.6 Gm. and the globulin from 1.7 to 3.3 Gm.

15. Eichelberger, L., and McCluskey, K. L.: Chemical Studies in Tuberculosis: Plasma Proteins, Cholesterol and Corpuscle Volume, *Arch. Int. Med.* 40:831-839 (Dec.) 1927. Wiener, H. J., and Wiener, R. E.: Plasma Proteins, *ibid.* 46:236-265 (Aug.) 1930. Peters and Eisenman.^{13c}

In 4 the albumin concentration was less than 3.5 Gm. per hundred cubic centimeters. Thus, the reduction in the levels of serum albumin and total serum protein is not entirely dependent on the urinary loss of

TABLE 3.—*Range of Values for Blood Serum Proteins in Cases of Amyloidosis*

Case	Total Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin/Globulin Ratio
1.....	5.8-7.0	3.0-4.6	2.4-2.8	1.1-1.8
2.....	5.6-6.5	3.0-3.9	2.6-2.6	1.1-1.5
3.....	6.7-7.2	4.3-4.5	2.2-3.2	1.3-2.0
4.....	5.9-7.1	3.0-4.5	2.6-2.9	1.1-1.7
5.....	6.2-6.4	3.7-3.8	2.5-2.6	1.4-1.5
6.....	6.2-6.7	3.6-4.4	2.3-2.6	1.4-2.0
7.....	6.0-6.5	3.4-4.1	2.4-2.6	1.3-1.7
8.....	6.6-7.0	3.9-4.6	2.4-4.6	1.4-2.0
9.....	6.1	3.7	2.4	1.5
10.....	5.8-6.9	3.0-4.7	2.2-2.7	1.1-2.1
11.....	6.6-7.1	4.1-4.8	2.3-2.5	1.6-2.1
12.....	5.2-6.4	2.6-3.2	2.6-3.2	1.0-1.0
13.....	5.8-8.0	2.4-4.1	1.7-3.4	0.8-2.3
14.....	6.3-7.0	3.3-3.9	2.4-3.2	1.1-1.6
16.....	7.0	4.1	2.3	1.7
17.....	5.0-7.2	2.4-3.5	2.3-2.8	1.1-1.4
18.....	6.4-6.6	4.0	2.4-2.6	1.5-1.6
19.....	6.3-7.0	3.7-4.5	2.1-2.6	1.4-1.9
20.....	6.6-7.5	4.0-4.6	2.3-2.6	1.6-2.0
21.....	5.9-6.2	3.0-3.6	2.6-2.9	1.1-1.4
22.....	6.0	3.4	2.6	1.3
A5.....	5.3	2.7	2.6	1.1
A6.....	6.1	3.1	2.8	1.1
A13.....	6.0	2.9	3.1	0.9
A16.....	6.8	4.0	2.5	1.6
A27.....	6.4	4.0	2.4	1.6
A30.....	6.0-6.6	3.4-4.3	2.3-2.6	1.3
A56.....	6.0	3.4	2.6	1.3
A59.....	6.0-6.8	3.2-4.4	2.4-2.8	1.2-1.8
A68.....	5.8-6.0	2.9-3.3	2.2-2.9	1.0-1.5
A78.....	6.2	3.7	2.5	1.5
31 cases.....	5.0-8.0 10 below 6	2.4-4.8 24 below 4 18 below 3.5	1.7-4.6 5 above 3	0.8-2.3

TABLE 4.—*Range of Values for Blood Serum Proteins in Cases of Amyloidosis without Albuminuria*

Case	Total Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin/Globulin Ratio
3.....	6.7	4.5	2.2	2.0
7.....	6.0-6.5	3.4-4.1	2.4-2.6	1.3-1.7
8.....	6.6-7.0	3.9-4.6	2.4-2.7	1.4-2.0
13.....	6.2-6.3	2.4-4.0	1.7-3.3	0.8-2.3
14.....	7.0	3.3	3.2	1.0
16.....	7.0	4.1	2.3	1.7
A6.....	6.1	3.1	2.8	1.1
.	6.0-7.0	2.4-4.6 5 below 4 4 below 3.5	1.7-3.3 2 above 3	0.8-2.3

albumin. It was likewise unrelated to any dietary factors, since all patients in both groups received a high protein diet that was well tolerated. As the decrease in the serum concentration of albumin and total proteins cannot be ascribed to chronic tuberculosis per se, to proteinuria or to malnutrition, we may conclude that such changes are the result of a diffuse hepatic injury secondary to the deposition of amyloid.

The range of fibrinogen concentration was approximately the same among both the patients with amyloidosis and those without amyloidosis, i. e., 0.2 to 0.7 Gm. per hundred cubic centimeters. The average for both groups was 0.41 Gm. The increase observed in most cases was consistent with the state of the chronic infection. The number of patients studied was insufficient to permit evaluation of the results.

TAKATA-ARA REACTION

The Takata-Ara reaction was originally introduced by Takata¹⁶ in 1925 as an aid in the differential diagnosis of lobar pneumonia and bronchopneumonia. Later he and Ara¹⁷ applied it to cerebrospinal fluid to differentiate bacterial from syphilitic meningitis. In 1930 Jezler¹⁸ employed the test in the study of parenchymatous diseases of the liver. At first it was felt that the Takata-Ara reaction was specific for cirrhosis of the liver, but it has been found positive in a large variety of hepatic diseases. The numerous attempts to correlate this reaction with other tests of liver function have so far met with failure.¹⁹ Snell and Magath⁵ found that about half of their patients with hepatic disease gave a positive reaction but pointed out that a large number of positive results were obtained when no other evidence of hepatic disease was found. Kirk²⁰ expressed the belief that "the Takata-Ara reaction is likely to be positive in any disease within which the globulin level is elevated," while Gros²¹ confirmed the opinion that the results of the test depended on the reversal of the albumin-globulin ratio in favor of the globulin.

16. Takata, M.: Ueber eine kolloidchemische Sero-Diagnostik der Lungenentzündung, *Far East. A. Trop. Med.*, Tr. Sixth Cong. **1**:693-699, 1925.

17. Takata, M., and Ara, K.: Ueber eine neue kolloidchemische Liquorreaktion und ihre practischen Ergebnisse, *Far East. A. Trop. Med.*, Tr. Sixth Cong. **1**:667-671, 1925.

18. Jezler, A.: Die Takatasche Kolloidreaktion in serum und Körperflüssigkeiten und ihre Beziehungen zu Störungen des Eiweisstoffwechsels der Leber, *Ztschr. f. klin. Med.* **114**:379-756, 1930.

19. Schindel, L., and Barth, E.: Die Bedeutung der Takata Reaktion für die Diagnose der Leberkrankungen in ihrem Verhältnis zur Galaktose und Bilirubin-Belastung, *Klin. Wchnschr.* **13**:1332-1335 (Sept. 15); 1335-1339 (Sept. 22) 1934. Magath, T. B.: The Takata-Ara Test of Liver Function, *Proc. Staff Meet., Mayo Clin.* **10**:493-496 (July 31) 1935. Heath, C., and King, E.: The Takata-Ara Test in the Diagnosis of Liver Disease, *New England J. Med.* **211**:1077-1081 (Dec. 13) 1934. Regins, A. B.: The Value of the Takata-Ara Reaction as a Diagnostic and Prognostic Aid in Cirrhosis of the Liver, *J. Lab. & Clin. Med.* **20**:902-913 (June) 1935. Chasnoff, J., and Solomon, S.: Takata-Ara Reaction: I. Clinical Significance, *ibid.* **23**:887-894 (June) 1938.

20. Kirk, R. C.: The Takata-Ara Test and Its Relation to Cirrhosis of the Liver, *J. A. M. A.* **107**:1354-1357 (Oct. 24) 1936.

21. Gros, W.: Das Bluteiweissbild und seine Bedeutung für den Mechanismus der Takata-Reaction, *Ztschr. f. d. ges. exper. Med.* **101**:519-551, 1937.

Simultaneous determination of the protein fractions and the Takata-Ara reaction were made in 30 instances for 16 patients with amyloidosis. The results (table 5) in general are similar to those reported by Taran and Lipstein²² for another group of patients from our hospital. The reaction was positive on the first determination in 7 instances and persistently negative in 2. In 7 the reaction was first negative but subsequently became positive and remained so in later determinations.

TABLE 5.—*Relation of Takata-Ara Reaction to Blood Serum Proteins*

Case.....	Takata-Ara Reaction	Total Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin/ Globulin Ratio
1.....	+	5.8	3.0	2.8	1.1
2.....	+	6.5	3.9	2.6	1.5
3.....	0	6.7	4.5	2.2	2.0
	+	7.2	4.0	3.2	1.3
4.....	0	7.1	4.5	2.6	1.7
	+	6.7	3.9	2.8	1.4
5.....	0	6.7	4.4	2.3	1.9
	0	6.3	3.9	2.4	1.6
	+	6.2	3.6	2.6	1.4
7.....	+	6.0	3.4	2.6	1.3
12.....	+	6.3	3.2	3.2	1.0
13.....	0	7.0	3.1	2.9	1.4
	0	5.8	3.4	2.4	1.4
	0	6.2	3.5	2.7	1.3
	+	6.2	3.6	2.6	1.4
	+	6.2	3.5	2.7	1.3
	+	6.1	3.5	2.6	1.4
14.....	+	6.4	3.8	2.6	1.5
17.....	0	6.2	3.6	2.6	1.4
	+	5.5	3.2	2.3	1.4
	+	6.4	4.0	2.4	1.7
A5.....	+	5.3	2.7	2.6	1.0
A27.....	0	6.4	4.0	2.4	1.7
A30.....	0	6.5	4.1	2.4	1.7
	0	6.6	4.3	2.3	1.8
	+	6.0	3.4	2.6	1.3
A33.....	0	6.8	4.6	2.2	2.1
	+	4.2	3.5	2.7	1.3
A68.....	0	5.8	3.3	2.5	1.3
A78.....	+	6.2	3.7	2.5	1.5

The albumin concentration was generally lowered; the globulin level was in the higher range of normal, and the albumin-globulin ratio was lowered. In 2 cases in which a negative and then a positive reaction was obtained, the change to positivity occurred with no appreciable alteration of the protein partition. The Takata-Ara reaction is positive as often with amyloidosis as with cirrhosis of the liver and is of no value in differential diagnosis. Its validity as a test of hepatic function is questioned.

22. Taran, A., and Lipstein, S.: Takata-Ara Reaction in Amyloidosis, *J. Lab. & Clin. Med.* **24**:479-484 (Feb.) 1939.

DEXTROSE TOLERANCE

Mann and Magath's²³ experimentally established fact that one of the most important functions of the liver is the maintenance of a normal blood sugar level has been clinically confirmed by the finding of hypoglycemia in patients with diffuse parenchymal damage of the liver.²⁴ Because of the great reserve capacity of the liver, some²⁵ question the sensitivity of the dextrose tolerance determination as a test of liver function. Recent reports,²⁶ however, indicate that it is of value.

The normal configuration of the dextrose tolerance curve and the variations due to impaired utilization of sugar are well known. After administration of an adequate amount of dextrose (100 Gm.) by mouth, the glycemic peak is reached in twenty to forty minutes²⁷ and returns to the fasting level by the end of the second hour. When carbohydrate metabolism is impaired the peak is higher; it is reached by the end of

23. Mann, F. C.: Studies in the Physiology of the Liver: I. Technic and General Effects of Removal, *Am. J. M. Sc.* **161**:37-42 (Jan.) 1921. Mann, F. C., and McGath, T. B.: The Effect of Removal of the Liver on the Blood Sugar Level, *Arch. Int. Med.* **30**:73-84 (July) 1922. Mann, F. C.: Effects of Complete and Partial Removal of the Liver, *Medicine* **6**:419-511 (Dec.) 1927.

24. Minot, A. S., and Cutler, J. T.: Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, *J. Clin. Investigation* **6**:369-402 (Dec.) 1928. Wilder, R. M., in discussion on Howard, C. P.: Incidence and Clinical Diagnosis of Acute Yellow Atrophy of the Liver, *Tr. A. Am. Physicians* **42**:141-163, 1927. Cross, J. B., and Blackford, L. M.: Fatal Hepatogenic Hypoglycemia Following New Arsphenamine, *J. A. M. A.* **94**:1739-1743 (May 31) 1930. Joseph, H.: Spontaneous Hypoglycemia in Childhood, *Am. J. Dis. Child.* **38**:346-357 (Oct.) 1929. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, *Arch. Int. Med.* **44**:700-711 (Nov.) 1929. Crawford, W. H.: Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver, *Am. J. M. Sc.* **181**:496-502 (April) 1931. McIntosh, R.: Acute Phosphorus Poisoning: Report of Case with Recovery, *Am. J. Dis. Child.* **34**:595-602 (Oct.) 1927. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Spontaneous Hypoglycemia: Two Cases with Fatty Metamorphosis of the Liver, *Am. J. Surg.* **24**:345-363 (May) 1934. Moore, H.; O'Farrell, W. R., and Headon, M. F.: Spontaneous Hypoglycemia Associated with Hepatitis, *Brit. M. J.* **1**:225-227 (Feb. 10) 1934.

25. Snell and Magath.⁵ Weir.⁷

26. Collier, F. A., and Jackson, H. C.: Surgical Aspects of Hypoglycemia Associated with Damage to the Liver, *J. A. M. A.* **112**:128-134 (Jan. 14) 1939. Lande, H., and Pollack, H.: Hyperglycemia and Glycosuria Associated with Disease of Biliary Tract, *Arch. Int. Med.* **56**:1097-1109 (Dec.) 1935.

27. Mosenthal, H. O.: The Interpretation of Sugar Tolerance Tests, *M. Clin. North America* **9**:549-574 (Nov.) 1925. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 1. Watson, B. A.: Normal Glucose Tolerance Tests, *J. Lab. & Clin. Med.* **23**:364-369 (Jan.) 1938.

the second hour, and the return to the fasting level is delayed until the end of the third or fourth hour.

One hundred grams of dextrose in black coffee was administered to each of 16 chronically tuberculous patients with clinically proved amyloidosis after an overnight fast. Blood sugar determinations were made by the Folin-Wu method on the specimens obtained during fasting and on those obtained every half-hour for two and a half hours after the sugar solution was consumed. Tolerance curves were similarly obtained for 13 tuberculous patients with no evidence of amyloid disease who served as controls. The results in this group were entirely within normal limits. This is contrary to the contention of some workers²⁸ that pulmonary tuberculosis per se causes a decrease in carbohydrate tolerance.

Table 6 summarizes the data for both groups of patients. The values for fasting blood sugar of all but 1 of the patients were in the normal range, of 60 to 100 mg. per hundred cubic centimeters. There was a definite abnormality of the curves of 10 of the patients with amyloidosis, while 6 had curves within normal limits. These data are plotted in the chart. The shaded area represents the limits of the curves for normal persons, and the clear area bounded by the joined circles shows the limits of the curves for patients with amyloidosis. Abnormal tolerance is evidenced by the prolongation of the period of hyperglycemia, by the tendency for the peak to occur at a later time interval than might be normally expected and by the failure of the blood sugar to return to a level of 120 mg. by the end of two and one-half hours.

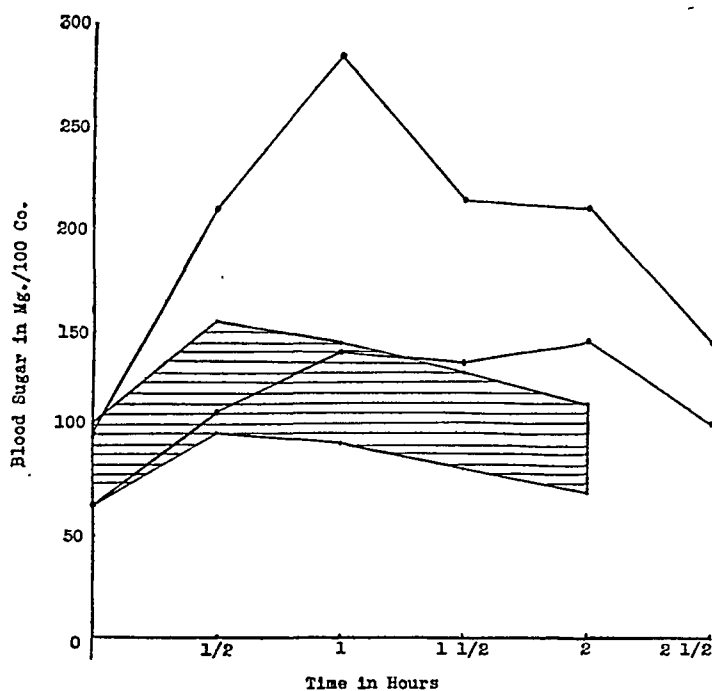
Decreased dextrose tolerance has been reported to occur in a number of conditions, among them obesity, diabetes mellitus, hyperthyroidism, toxemia, acute infection and diffuse parenchymatous disease of the liver. There was not any obese patient in our group, nor did any patient at any time manifest symptoms or signs of hyperthyroidism or diabetes mellitus. Postprandial glycosuria was frequently tested for but was never found. It has been established experimentally and clinically²⁹ that toxemia and acute infections diminish carbohydrate metabolism.

28. Dalto, A.: La glucemia en relación con la eritrosedimentación en tuberculosis pulmonar, *Prensa méd. argent.* **24**:859-879 (April 28) 1937. Silveira, J., and de Figueiredo, J.: A glicemia nos tuberculosos pulmonares, *Bahia med.* **9**:103-106 (June) 1938. Banks, Sprague and Snell.⁹

29. Williams, J. L., and Dick, G. F.: Decrease Dextrose Tolerance in Acute Infectious Diseases, *Arch. Int. Med.* **50**:801-818 (Dec.) 1932. Soskin, S.; Allweiss, M. D., and Mirsky, I. A.: Interpretation of Abnormal Glucose Tolerance Curves Occurring in Toxemia in Terms of Liver Function, *ibid.* **56**:927-934 (Nov.) 1935. Sweeney, J. S., and Lackey, R. W.: Effect of Toxemia on Tolerance for Dextrose, *ibid.* **41**:257-263 (Feb.) 1928. Sweeney, J. S.: Effect of Toxemia on Tolerance of Glucose and on Action of Insulin, *ibid.* **41**:420-427 (March) 1928. Sweeney, J. S.; Barshop, N., and LoBello, L. C.: Effect of Toxemia on Tolerance and Action of Insulin, *ibid.* **53**:689-698 (May) 1934.

TABLE 6.—*Blood Sugar Tolerance Curve in Cases of Amyloidosis, Mg./100 Cc.*

Case	Fasting	½ Hour	1 Hour	1½ Hours	2 Hours	2½ Hours
1.....	80	110	160	175	210	...
2.....	95	160	170	...	175	135
3.....	70	140	140	160	155	105
4.....	100	210	284	215	180	...
5.....	65	115	125	135	150	105
6.....	60	155	170	...	190	145
7.....	90	110	140	...	160	145
8.....	95	150	220	...	195	115
10.....	95	140	165	...	145	...
14.....	100	190	170	...	155	105
	60-100	110-210	125-284	135-215	145-210	105-145
9.....	75	100	125	...	95	...
11.....	80	140	135	...	75	85
12.....	75	105	130	...	115	110
13.....	105	145	120	...	115	60
15.....	100	110	125	...	90	...
16.....	95	110	125	...	120	75
	75-105	100-145	120-135	75-115	60-110
13 controls.....	65-105	100-150	95-145	85-130	70-115



Dextrose tolerance curves for normal persons and for patients with amyloidosis. The shaded area denotes the limits of the curves for normal persons. The area bounded by the joined circles indicates the limits of the curves for patients with amyloidosis.

In pulmonary tuberculosis, however, persistently normal values for fasting blood sugar have been noted.³⁰ Kramer³¹ studied 100 patients

30. Bilbao Lumbreras, R., and Franco Morante, A.: Colesterinemia y glicemia en los enfermos tuberculosos, *Arch. de med., cir. y especialid.* **37**:1365-1373 (Dec. 15) 1924. Mazzetti, M.: L'equilibrio glicemico a digiuno nella tubercolosi polmonare cronica, *Tuberculosi* **29**:245-258 (July) 1937.

31. Kramer, D. W.: Glucose Tolerance Curves in Pulmonary Tuberculosis. *J. Lab. & Clin. Med.* **18**:1212-1220 (Sept.) 1933.

with chronic tuberculosis by means of the dextrose tolerance test, using the technic previously described in this report, and concluded that the tendency in tuberculosis is toward an increased rather than a decreased tolerance. This is in agreement with the findings in our control group.

Coller and Troost³² were able to produce high plateau curves, similar to those found in patients with diabetes mellitus, after experimental hepatic damage. Clinically they observed this type of curve in patients with various diffuse degenerate and destructive diseases of the liver. Conn and his co-workers³³ found diminished carbohydrate tolerance, due to impaired glycogenesis, in chronic infectious hepatitis and also demonstrated impaired glycogenolysis by producing hypoglycemia on restricted carbohydrate intake. While no effort was made to study the glycolytic function in our patients, low fasting sugar levels have been observed.

It was not possible to correlate abnormal tolerance with age, sex, state of nutrition or presence of tuberculous enterocolitis or nephrosis. Difficulty of early diagnosis makes it impossible to be certain of the duration of amyloid disease in any single case. The extent of pathologic involvement is likewise not known. The wide fluctuation of the fasting and postprandial levels of blood sugar and the prolonged plateau nature of the curve point to hepatic dysfunction as a possible source of the abnormality.

BLOOD CONSTANTS

Hematocrit studies reveal that a hyperchromic macrocytic anemia, similar in some respects to pernicious anemia, is a frequent accompaniment of diffuse hepatic damage.³⁴ A satisfactory explanation for this picture is lacking. In pernicious anemia, the significant defect is an inability to carry out some essential step in gastric digestion, and thus the lack of a substance which the normal person can derive from ingested food produces the clinical syndrome. Meulengracht³⁵ advanced the

32. Coller, F. A., and Troost, F. L.: Glucose Tolerance and Hepatic Damage, *Ann. Surg.* **90**:781-793 (Oct.) 1929.

33. Conn, J. W.; Newburgh, L. H.; Johnston, M. W., and Sheldon, J. M.: Study of the Deranged Carbohydrate Metabolism in Chronic Infectious Hepatitis, *Arch. Int. Med.* **62**:765-782 (Nov.) 1938.

34. Wintrobe, M. M., and Shumacker, H. B.: The Occurrence of Macrocytic Anemia in Association with Disorder of the Liver, *Bull. Johns Hopkins Hosp.* **52**:387-407 (June) 1933. Goldhamer, S. M.: Liver Extract Therapy in Cirrhosis of the Liver, *Arch. Int. Med.* **53**:54-57 (Jan.) 1934. Cheney, G.: The Morphology of the Erythrocytes in Cirrhosis and Other Disorders of the Liver, *California & West. Med.* **39**:90 (Aug.) 1933. Higgins, G. M., and Stasney, J.: Macrocytic Anemia in Experimental Cirrhosis, *Proc. Staff Meet., Mayo Clin.* **10**:429-432 (July 3) 1935.

35. Meulengracht, E.: *Der chronische hereditäre hämolytische Ikterus*, Leipzig, W. Klinkhardt, 1922, p. 27.

hypothesis that swelling of erythrocytes due to alteration in blood plasma and osmotic pressure is the cause of these changes. Rosenberg and Walters³⁶ rejected this explanation and agreed with Capps³⁷ that such changes are probably due to abnormal red cell development and like Wintrobe³⁸ expressed the belief that this results from deficient storage or utilization of the necessary hematopoietic principle. Schiff and his associates,³⁹ however, offered proof that the diseased liver does contain the specific hemopoietic substance and suggested that the cause of macrocytosis is not a failure of storage. Yet the association of this hematologic picture with hepatic disease is so characteristic that when it occurs in the presence of free hydrochloric acid in the stomach some investigators⁴⁰ believe it is confirmatory evidence of hepatic damage.

The blood constants of 18 patients with amyloidosis were studied. The method used was as follows: Approximately 10 cc. of venous blood was withdrawn from the antecubital vein without stasis. Half of the blood was added to a known amount of a 1.1. per cent solution of potassium oxalate in the proportion of 5 parts of blood to 1 part of solution. The exact amount of blood was calculated from the total volume in the accurately calibrated centrifuge tube. The mixture was immediately centrifuged for thirty minutes at 3,000 revolutions per minute, and the packed red cell volume was recorded. The remaining 5 cc. of blood was prevented from clotting by the addition of a few crystals of potassium oxalate and was used for repeated counts of red cells, colorimetric determination of hemoglobin (Hellige-wedge) and enumeration of reticulocytes (brilliant cresol blue).

A summary of the findings is shown in table 7. Twelve of the 18 patients showed macrocytosis, as indicated by mean corpuscular volumes, which ranged from 97 to 127 cubic microns. Five had normocytosis and only 1 microcytosis. In 12 cases the red cell count was below normal, and in the remaining 6 it was 4,500,000 or above. In only 2 instances, however, was the count below 3,000,000, a fact indicating that a marked degree of anemia is not common in patients with amyloidosis. Of the 12 patients exhibiting macrocytosis, 6 had a slightly increased color index and mean corpuscular hemoglobin, while 6 had values in the normal range. The patients with no macrocytosis showed

36. Rosenberg, D. H., and Walters, A.: Macrocytic Anemia in Liver Disease, Particularly Cirrhosis, *Am. J. M. Sc.* **192**:86-97 (July) 1936.

37. Capps, J. A.: A Study of Volume Index: Observations upon the Volume of Erythrocytes in Various Disease Conditions, *J. M. Research* **10**:367-401, 1903.

38. Wintrobe, M. M.: Relation of Disease of the Liver to Anemia, *Arch. Int. Med.* **57**:289-306 (Feb.) 1936.

39. Schiff, L.; Rich, M. L., and Simon, S. D.: The "Haemopoietic Principle" in the Diseased Human Liver, *Am. J. M. Sc.* **196**:313-321 (Sept.) 1938.

40. Van Duyn, J.: Macrocytic Anemia in Disease of the Liver, *Arch. Int. Med.* **52**:839-851 (Dec.) 1933. Snell and Magath.⁵

a normocytic normochromic blood picture. All of the patients had an initial reticulocyte percentage ranging from 0.2 to 3. The peripheral smear gave evidence of active erythropoiesis in every case.

The reticulocyte response to liver extract was studied for 10 patients with initial macrocytosis and for 5 with normocytosis, without regard for the red cell level. Two cubic centimeters of concentrated liver extract⁴¹ was injected intramuscularly every third day and the reticulocyte count made simultaneously. The degree of reticulocytosis to be expected in any single case depends on the initial reticulocyte level at the time therapy is started. At a level of 3,000,000 red cells the response is

TABLE 7.—*Blood Constants in Cases of Amyloidosis*

Case No.	Sex	Liver Edge Palpable*	Volume of Red Blood Cells, Cc. per 100 Cc.	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin Concentration		Mean Corpuscular Hemoglobin, Micrograms	Color Index	Mean Corpuscular Volume, Cu. Microns	Reticulo-cytes, Per-cent-age	Maxi-mum Rise in Reticulo-cytes, Per-cent-age
					Gm. per 100 Cc.	Per-cent-age					
Normal	male.....		40-54	16.7	100	27-32	1.0	80-94	0.5-2	
	female.....		37-47								
1	M	4 F	38.5	4,100,000	9.5	57	23.0	0.7	94	0.3	2.1
2	M	4 F	37.0	3,000,000	10.7	65	36.0	1.0	119	1.8	2.1
3	M	C M	43.0	3,700,000	13.5	81	37.0	1.1	116	0.9	1.6
4	M	5 F	37.2	3,500,000	9.5	57	27.2	0.8	107	0.2	...
5	M	2 F	46.3	3,800,000	13.7	83	36.0	1.1	121	0.8	3.5
6	M	1 F	39.6	3,200,000	10.7	65	33.3	1.0	123	0.2	1.2
9	M	Not palpable	38.6	4,500,000	10.5	63	30.7	0.7	86	0.5	4.0
10	F	2 F	34.6	3,900,000	11.0	66	28.0	0.8	89	0.5	2.4
13	M	C M	49.6	6,100,000	15.0	90	24.2	0.9	80	0.2	...
14	F	4 F	45.0	4,500,000	14.0	84	31.0	0.9	100	1.0	2.0
18	M	4 F	45.6	4,800,000	13.2	80	26.6	0.8	92	0.2	1.6
19	M	4 F	40.9	5,300,000	11.0	67	27.2	0.6	77
20	M	3 F	33.7	2,600,000	7.9	42	26.9	0.8	127	0.4	8.0
21	M	C M	47.0	4,000,000	11.5	69	29.0	0.9	117	1.0	4.0
22	M	4 F	25.0	2,400,000	8.5	50	35.4	1.0	104	0.8	4.6
23	M	1 F	49.4	4,700,000	14.2	86	30.0	0.9	109	0.3	2.7
24	F	1 F	40.8	3,600,000	12.7	77	35.0	1.0	113	3.0	3.8
25	F	1 F	36.2	3,700,000	12.0	72	32.0	0.9	97	1.0	2.8

* The following abbreviations are used: F, fingerbreadths, and C M, costal margin.

slight and variable, and the percentage may reach about 4. At a level of 2,500,000 red cells about 7 is considered adequate, and at a level of 2,000,000 red cells it should be about 12.⁴² The peak of reticulocytosis is generally reached at the fifth to the ninth day and is completed in three weeks.

The response in all but 2 patients was variable and uncertain. This may be related to the relatively high initial red cell level in these patients. In the 2 just mentioned, the initial level of red cells was 2,400,000 and

41. Lederle concentrated liver extract, 15 units per cubic centimeter, was used.

42. Minot, G. H.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract, *Am. J. M. Sc.* **175**:599-621 (May) 1928. Minot, G. H.; Murphy, W. P., and Stetson, R. P.: Response of Reticulo-cytes to Liver Therapy, *ibid.* **175**:581-598 (May) 1928. Wakerlin, G. E.: Hemopoietic Liver Principle, *Ann. Int. Med.* **11**:31-38 (July) 1937.

2,600,000, respectively. In the former, with a color index of 1.0 and a mean corpuscular volume of 104 cubic microns, there was no constant reticulocytosis, while in the latter, with a color index of 0.8 and a mean corpuscular volume of 127 cubic microns, a percentage of 8 was reached on the seventh day. The latter patient, however, died before further studies could be undertaken. In all instances but 1 liver extract was well tolerated, and, despite the lack of hematologic improvement the patients had a sense of well-being while under treatment.

From a limited experience with liver extract therapy in amyloidosis, it has not been possible to demonstrate the exact defect that is responsible for the change in blood cell volume. The presence of macrocytosis in so high a proportion of the patients studied does, however, indicate that hepatic damage is present in persons with this disease.

SUMMARY AND CONCLUSIONS

The effect of amyloid infiltration on the functional capacity of the liver was studied by means of eight different laboratory tests. Amyloidosis was secondary to chronic pulmonary tuberculosis and was clinically determined by the following criteria: the presence of albuminuria, cylindruria and an enlarged palpable liver and 100 per cent absorption (disappearance) of congo red from the blood in thirty minutes.

The icterus index, the galactose tolerance and the urinary urobilinogen excretion were consistently normal.

Two of 12 patients showed slightly abnormal bromsulphalein absorption (5 per cent retention at the end of thirty minutes).

The total blood serum proteins were definitely reduced as a result of a fall in the albumin concentration. These reductions were demonstrated in some cases before there was any urinary loss of proteins. The relation of serum proteins to hepatic damage is discussed.

The Takata-Ara reaction was of no diagnostic value in amyloidosis.

Diminished dextrose tolerance probably due to impaired hepatic glycogenesis was demonstrated in 10 of 16 patients. The glycogenolytic function was not studied.

Macrocytosis was present in 12 of 18 of the patients. This was associated with slight hyperchromia in 6 and with normochromia in 6. Of 2 patients in whom the initial blood count was below 3,000,000, only 1 responded to a course of liver extract therapy with an adequate reticulocytosis.

The determinations in the chemical studies of the blood were performed by Mr. Al Taran.

Progress in Internal Medicine

INFECTIOUS DISEASES

A REVIEW OF SIGNIFICANT PUBLICATIONS IN 1940-1941

HOBART A. REIMANN, M.D.

PHILADELPHIA

A review of the advances in knowledge pertaining to infectious diseases during the past year covers a wide range of subjects, as usual. Therapy with sulfanilamide and its derivatives again commands the most interest. Of outstanding importance also is the recognition of new forms of disease of the respiratory tract, which are among the commonest afflictions of mankind. Consequently, the most space has been devoted to these subjects. Such diseases as histoplasmosis,¹ fusospirochetosis² and leptospirosis,^{2a} which recently have been adequately summarized, need no further discussion here.

THERAPY WITH SULFANILAMIDE AND ITS DERIVATIVES

Since this review deals primarily with significant advances in the knowledge of infectious diseases and related subjects, the bulk of papers on therapy with sulfanilamide and its derivatives published in the past year is not considered. Only new facts, new views and changes in previous views are discussed. Good summaries have already been published by Carey³ in respect to chemotherapy in pediatric practice, by Lockwood⁴ in surgical practice and by Long⁵ in general medicine. Long's

From the Jefferson Medical College Hospital.

1. Meleney, H. E.: Histoplasmosis (Reticulo-Endothelial Cytomycosis): A Review, *Am. J. Trop. Med.* **20**:603-616 (July) 1940.

2. Shirazy, E.: Fusospirochetosis (Vincent's Disease), *Internat. Clin.* **2**:115-140 (June) 1940.

2a. Ashe, W. F.; Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's Disease: A Complete Review of American Literature and an Abstract of the World Literature; Seven Case Reports, *Medicine* **20**:145-210 (May) 1941.

3. Carey, B. J.: Use of Sulfanilamide and Related Compounds in Diseases of Infancy and Childhood, *J. A. M. A.* **115**:924-929 (Sept. 14) 1940.

4. Lockwood, J. S.: Sulfanilamide in Surgical Infections, *J. A. M. A.* **115**:1190-1195 (Oct. 5) 1940.

5. Long, P. H.: The Clinical Use of Sulfanilamide and Its Derivatives in the Treatment and Prophylaxis of Certain Infections, *Bull. New York Acad. Med.* **16**:732-750 (Dec.) 1940.

review contains numerous simplified charts showing those diseases in which chemotherapy is of established value, those in which it is of doubtful value and those in which it is of no value. Charts and tables also conveniently outline the dosage of various compounds administered by various routes and their toxic reactions.

Sulfathiazole (2-[paraaminobenzenesulfamido]-thiazole) has been accepted for inclusion in New and Nonofficial Remedies by the Council on Pharmacy and Chemistry, and two newly synthesized compounds, sulfadiazine (2-[paraaminobenzenesulfamido]-pyrimidine)⁶ and sulfaguanidine (sulfanilylguanidine)⁷ are under trial. Sulfadiazine has several apparent advantages over sulfathiazole, particularly in the treatment of pneumonia⁸: Acetylation is slight; the drug diffuses readily into pleural, ascitic and cerebrospinal fluids, and it remains longer at a high level in the blood. Besides, it is readily absorbed in most cases; it is eliminated by the kidneys, and its toxicity is relatively low.

Sulfaguanidine, synthesized by Marshall and his aids,⁷ is a water-soluble compound which is poorly absorbed from the digestive tract. Therefore, because of its high concentration in the bowel and its low concentration in the blood, it may be particularly suited to combat intestinal infection. Firor reported at a meeting of the Southern Surgical Association that the bacterial count in the intestine was reduced by its use. The drug may prove to be of value in preventing postoperative infections of abdominal wounds and in treating intestinal diseases. Marshall and associates⁹ and Lyon¹⁰ used sulfaguanidine in treating

6. Roblin, R. O., Jr.; Williams, J. H.; Winnek, P. S., and English, J. P.: Chemotherapy: II. Some Sulfanilamido Heterocycles, *J. Am. Chem. Soc.* **62**: 2002-2005 (Aug.) 1940. Long, P. H.: Sulfadiazine: The 2-Sulfamidopyrimidine Analogue of Sulfanilamide, *J. A. M. A.* **116**:2399-2400 (May 24) 1941.

7. Marshall, E. K., Jr.; Bratton, A. C.; White, H. J., and Litchfield, J. T.: Sulfanilylguanidine: A Chemotherapeutic Agent for Intestinal Infections, *Bull. Johns Hopkins Hosp.* **67**:163-188 (Sept.) 1940.

8. Plummer, N., and Ensworth, H. K.: Absorption and Excretion of Sulfadiazine, *Proc. Soc. Exper. Biol. & Med.* **45**:734-738 (Nov.) 1940. Reinhold, J. G.; Flippin, H. F.; Schwartz, L., and Domm, A. H.: The Absorption, Distribution and Excretion of 2-Sulfanilamido Pyrimidine (Sulfapyrimidine, Sulfadiazine) in Man, *Am. J. M. Sc.* **201**:106-117 (Jan.) 1941. Sadusk, J. F., and Tredway, J. B.: Observations on the Absorption, Excretion, Diffusion and Acetylation of Sulfadiazine in Man, *Yale J. Biol. & Med.* **13**:539-556 (March) 1941. Finland, M.; Straus, E., and Peterson, O. L.: Sulfadiazine: Therapeutic Evaluation and Toxic Effects on Four Hundred and Forty-Six Patients, *ibid.* **116**:2641-2647 (June 14) 1941.

9. Marshall, E. K., Jr.; Bratten, A. C.; Edwards, L. B., and Walker, E.: Sulfanilylguanidine in the Treatment of Acute Bacillary Dysentery in Children, *Bull. Johns Hopkins Hosp.* **67**:94-111 (Jan.) 1941.

10. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery: II. Clinical Use of Sulfanilylguanidine, *West Virginia M. J.* **37**:54-65 (Feb.) 1941.

children who had bacillary dysentery, with encouraging results. Unfortunately, experience with the drug in cases of idiopathic ulcerative colitis is not promising. Its use in treating carriers of typhoid bacilli has been suggested.¹¹

One must accept with caution unguarded, uncontrolled statements¹² that sprays of certain sulfanilamide compounds in solution are of value in the treatment of acute influenza and, what is even more dubious, that they serve as a preventive measure against influenza. The author whose work is referred to reports success in the treatment of chronic sinusitis with nasal sprays of sodium sulfathiazole. Spraying the solution into the nose, he claims, produces better results than instilling it into the sinuses. The report is unconvincing.

Inhibiting Substances.—The following substances have thus far been shown to inhibit the bacteriostatic action of sulfanilamide compounds¹³: (1) peptones (Lockwood), (2) certain fractions of streptococci (Stamp¹⁴), (3) certain fractions of *Brucella* (Green¹⁵), (4) certain coenzymes (West and Coburn¹⁶), (5) extracts of certain animal tissues (MacLeod¹⁷) and (6) extracts of yeast and paraaminobenzoic acid (Woods¹⁸). According to MacLeod, extracts of fresh normal muscle, pancreas and spleen contain inhibiting substances. The inhibition is greatly enhanced in autolyzed tissues. Similar substances are present in urine after acid hydrolysis and in pus, but not in serum. When a strain of pneumococci became drug fast production of the inhibiting substance was greatly increased.

One of the inhibiting substances has been identified. Woods's¹⁸ observation that paraaminobenzoic acid in high dilution inhibits the bac-

11. Levi, J. E., and Willen, A.: The Typhoid Carrier State Treated with Sulfa-guanidine, *J. A. M. A.* **116**:2258 (May 17) 1941.

12. Turnbull, F. M.: Intranasal Therapy with Sodium Salt of Sulfathiazole in Chronic Sinusitis, *J. A. M. A.* **116**:1899-1900 (April 26) 1941.

13. Strauss, E.; Lowell, F. C., and Finland, M.: Observations on the Inhibition of Sulfonamide Action by Para-Aminobenzoic Acid, *J. Clin. Investigation* **20**:189-197 (March) 1941.

14. Stamp, T. C.: Bacteriostatic Action of Sulphanilamide in Vitro: Influence of Fractions Isolated from Haemolytic Streptococci, *Lancet* **2**:10-17 (July 1) 1939.

15. Green, H. N.: The Mode of Action of Sulphanilamide with Special Reference to a Bacterial Growth-Stimulating Factor ("P" Factor) Obtained from *Br. Abortus* and Other Bacteria, *Brit. J. Exper. Path.* **21**:38-64 (Feb.) 1940.

16. West, R., and Coburn, A. F.: The Relationship of Sulfapyridine, Nicotinic Acid, and Coenzymes to the Growth of *Staphylococcus Aureus*, *J. Exper. Med.* **72**:91-97 (July) 1940.

17. MacLeod, C. M.: The Inhibition of the Bacteriostatic Action of Sulfonamide Drugs by Substances of Animal and Bacterial Origin, *J. Exper. Med.* **72**:217-232 (Sept.) 1940.

18. Woods, D. D.: The Relation of *p*-Aminobenzoic Acid to the Mechanism of the Action of Sulphanilamide, *Brit. J. Exper. Path.* **21**:74-90 (April) 1940.

teriostatic effect of sulfanilamide on the growth of hemolytic streptococci in vitro was confirmed by several investigators.¹⁹ Woods's theory regarding the mechanism of the action of sulfanilamide and its derivatives is not much different from that previously proposed, namely, that the inhibitors of growth (sulfanilamide compounds) are effective because they interfere with an "essential metabolite," a substance which is necessary for bacterial growth. Paraaminobenzoic acid also neutralizes the effects of such drugs on pneumococci.^{19b} According to Findlay,²⁰ paraaminobenzoic acid inhibited the effect of sulfanilamide on the virus of venereal lymphogranuloma. Since this virus, as well as the hypothetical one of trachoma, is the only one supposedly influenced by sulfanilamide, he suggests that only these two viruses need paraaminobenzoic acid for metabolism.

CHEMOTHERAPY OF COCCIC DISEASES

Pneumococcic Lobar Pneumonia.—The introduction of sulfadiazine was the only important advance in the past year in the treatment of this disease. All physicians agree as to the value of therapy of the disease with sulfanilamide and its derivatives, but, as usual, enthusiasm is overreaching and there is the expected tendency to treat all acute pulmonary infections with a sulfanilamide compound, regardless of the etiologic agent. The chemotherapy of pneumonia is reviewed by Finland,²¹ who cites nearly 150 papers published in 1939 and 1940. He and his associates²² emphasize the progress made in chemotherapy and point out that serotherapy as well is needed in treating certain severe forms of the disease. From statistical evidence it also appears that while the death rate is steadily diminishing, it has not decreased as rapidly as expected after the introduction of chemotherapy, which may mean that drugs are not used to their fullest extent in treatment of pneumococcic pneumonia. According to Plummer and his associates,²³ the use of antipneu-

19. (a) Landy, M., and Wyeno, J.: Neutralization (in Vitro) of Bacteriostatic Activity of Sulfonamides by *p*-Aminobenzoic Acid, *Proc. Soc. Exper. Biol. & Med.* **46**:59-62 (Jan.) 1941. (b) McCarty, M.: Effect of *p*-Aminobenzoic Acid on Therapeutic and Toxic Action of Sulfapyridine, *ibid.* **46**:133-136 (Jan.) 1941. (c) Strauss, Lowell and Finland.¹³

20. Findlay, G. M.: Action of Sulfanilamide on the Virus of Lymphogranuloma Venereum, *Brit. J. Exper. Path.* **21**:356-360 (Dec.) 1940.

21. Finland, M.: Report on Medical Progress: Treatment of Pneumonia, *New England J. Med.* **223**:499-506 (Sept. 26) 1940.

22. Finland, M.; Lowell, F. C., and Strauss, E.: Some Aspects of the Chemotherapy of Pneumonia, *New York State J. Med.* **40**:1115-1122 (July 15) 1940. Finland.²¹

23. Plummer, N.; Liebmann, J.; Solomon, S.; Kammerer, W. H.; Kalkstein, M., and Ensworth, H. K.: Chemotherapy Versus Combined Chemotherapy and Serum in the Treatment of Pneumonia: A Study of Six Hundred and Seven Alternated Cases, *J. A. M. A.* **116**:2366-2371 (May 24) 1941.

mococcus serum in addition to chemotherapy neither lowered the fatality rate nor hastened the speed of recovery. Serum, they say, is of use only in treating patients who cannot tolerate sulfanilamide compounds or those who do not respond to chemotherapy within twenty-four to forty-eight hours. No essential differences were noted in therapeutic response to sulfapyridine, sulfathiazole or sulfadiazine.

There are, on the other hand, many kinds of pneumonia which do not respond favorably to chemotherapy, and these, for the most part, cannot always be diagnosed from clinical data, without aid from laboratory data. In my experience ²⁴ in the winter of 1940-1941, in about two thirds of the cases of pneumonia the disease was regarded as non-pneumococcic and was not treated with drugs or with serum. In many cases the disease was that which is tentatively called "virus" pneumonia, discussed in a later section. Pneumococci of the higher numbered types (all those other than types I, II, III, V, VII, VIII and XIV) were occasionally found in the sputum in small numbers and had no relation to the pneumonia. Sulfathiazole used experimentally in a few cases had no effect on the disease.

It may be difficult, or impossible at times, even with assistance from the laboratory, to decide whether pneumococci found in the sputum are actually the cause of the pneumonia, and under these circumstances the attending physician may feel negligent if he does not use chemotherapy. He is justified in giving the appropriate drug, but if after a thorough trial under controlled conditions no benefit is apparent in thirty-six to forty-eight hours, the drug should be discontinued. The following generalizations are helpful: Pneumococci of types I or II when found in a case of pneumonia are almost always the cause of the disease; types III, V, VII, VIII or XIV are often the cause of it, and the other types may simply be inhabitants of the respiratory tract, without being implicated in the pneumonia. If in a case of the disease pneumococci of any type are found in great numbers in the sputum or are present in the blood or in foci of purulent infection, they are almost always the causative organisms. The nature of the clinical course, the increased number of leukocytes, the rapid sedimentation rate of erythrocytes and roentgenograms are helpful in diagnosis.

Flippin and his associates ²⁵ show that sulfadiazine is about as good as sulfathiazole in the treatment of pneumococcic pneumonia. It has certain advantages over sulfathiazole, as discussed on page 326.

24. Reimann, H. A.: Management of Pneumonias Associated with Pneumococci of the Higher Numbered Types, read at the meeting of the American College of Physicians, Boston, April 25, 1941.

25. Flippin, H. F.; Rose, S. B.; Schwartz, L., and Domm, A. H.: Sulfadiazine and Sulfathiazole in the Treatment of Pneumococcic Pneumonia: A Progress Report on Two Hundred Cases, *Am. J. M. Sc.* **201**:585-592 (April) 1941.

There appears to be a greater stimulation of immune bodies in patients whose pneumonia is treated with sulfathiazole rather than with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). This suggested to Kneeland and Mulliken²⁶ that sulfapyridine is a somewhat more powerful antipneumococcic agent than is sulfathiazole.

The development of specific agglutinins, the mouse-protective power and the result of the polysaccharide cutaneous test were studied in patients with pneumonia treated with serum and sulfapyridine, with sulfapyridine alone or without specific drugs.²⁷ In patients receiving sulfapyridine and serum the cutaneous reaction was positive, agglutinins were more frequently present and the mouse-protective power was greater than in those receiving sulfapyridine alone. The cutaneous reaction is a more reliable aid in determining the prognosis than is the presence of agglutinins or the mouse-protective power of the patient's serum. Type III pneumococcic infections are striking in that they seldom give rise to positive cutaneous reactions. Sulfapyridine was given to 2 patients with lobar pneumonia, in spite of concomitant leukopenia.²⁸ Both recovered.

Drug Fastness.—Pneumococci which are resistant to the inhibiting effects of one of the sulfanilamide compounds are also resistant to related ones. Thus, there is no reason to substitute one drug for another when fastness develops.²⁹ A test for detecting drug-fast pneumococci has been devised.³⁰ Plain blood agar plates and plates containing 10 mg. of a sulfanilamide compound are seeded and incubated as usual. Unchanged pneumococci will grow on the plain blood agar plate only; drug-fast pneumococci will grow on both plates.

Meningitis.—Coleman³¹ shows that the mortality rate from pneumococcic meningitis has been reduced from nearly 100 to about 35 per

26. Kneeland, Y., and Mulliken, B.: Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfathiazole, *J. Clin. Investigation* **19**:735-738 (Sept.) 1940.

27. Terry, L. L.; Thompson, L. D., and Edwards, J. C.: Immune Response in Drug Treated Cases of Pneumococcal Pneumonia, *Am. J. M. Sc.* **201**:574-584 (April) 1941.

28. Friedberg, C. K.: Sulfapyridine in Lobar Pneumonia with Leukopenia, *J. A. M. A.* **116**:270-272 (Jan. 25) 1941.

29. Schmidt, L. H.; Clausus, C. E., and Starks, E.: Response of Sulfapyridine-Fast Pneumococci to Sulfathiazole and Sulfamethylthiazole, *Proc. Soc. Exper. Biol. & Med.* **45**:256-259 (Oct.) 1940. Lowell, F. C.; Strauss, E., and Finland, M.: Observations on the Susceptibility of Pneumococci to Sulfapyridine, Sulfathiazole and Sulfamethylthiazole, *Ann. Int. Med.* **14**:1001-1023 (Dec.) 1940.

30. Cotter, H. Y.; Kirchner, M. T., and Romano, M.: Recognition of Sulfapyridine-Fast Pneumococci, *Proc. Soc. Exper. Biol. & Med.* **46**:241-244 (Feb.) 1941.

31. Coleman, F. H.: Pneumococcal Meningitis Since the Introduction of Sulfapyridine, *Lancet* **2**:615-618 (Nov. 16) 1940.

cent of chemotherapy. Rhoads and his associates³² report 7 recoveries in 22 consecutive cases. Neal and her associates³³ record 10 recoveries in 30 cases. No new facts have accrued regarding the treatment of meningococcic meningitis, except Banks's³⁴ evidence that sulfathiazole, in spite of theoretic shortcomings, is highly effective. Sulfadiazine is also of value.^{34a} Gregory and his associates³⁵ and Hoyne³⁶ both report good results with sulfanilamide given orally or parenterally. According to Hoyne, much of the decrease in mortality rate is due to the abandonment of intraspinal therapy or lumbar puncture, except for the first diagnostic examination. The important matter of the use of sulfanilamide compounds to rid carriers of meningococci has not yet been settled.

Subacute Bacterial Endocarditis.—Uncertainty still exists as to the value of chemotherapy in this infection. The results of a year's trial with combined treatment with heparin and a sulfanilamide compound are not encouraging. Dangerous complications, such as cerebral hemorrhage, and possibly acute glomerulonephritis, arise. Other methods, such as induction of artificial fever, which theoretically enhance the bacteriostatic action of the chemicals, have been suggested and tried, with encouraging results. One group favors the use of physically induced pyrexia,³⁷ while another employed typhoid vaccine³⁸ to raise the temperature. These procedures obviously are drastic methods of treatment of patients already gravely sick, but, as many agree, under favorable circumstances the value of any possible remedy is worth testing in the case of a disease which is almost invariably fatal. According to Lichtman

32. Rhoads, P. S.; Hoyne, A. L.; Levin, B.; Horswell, R. G.; Reals, W. H., and Fox, W. W.: Treatment of Pneumococcic Meningitis, *J. A. M. A.* **115**:917-922 (Sept. 14) 1940.

33. Neal, J. B.; Applebaum, E., and Jackson, H. W.: Sulfapyridine and Its Sodium Salt in the Treatment of Meningitis Due to the Pneumococcus and Hemophilus Influenzae, *J. A. M. A.* **115**:2055-2058 (Dec. 14) 1940.

34. Banks, H. S.: Sulfathiazole in Cerebrospinal Fever, *Lancet* **1**:104-107 (Jan. 25) 1941.

34a. Dingle, J. H.; Thomas, L., and Morton, A. R.: Treatment of Meningococcic Meningitis and Meningococcemia with Sulfadiazine, *J. A. M. A.* **116**:2666-2668 (June 14) 1941.

35. Gregory, K. K.; West, E. J., and Stevens, R. E.: Epidemic Cerebrospinal Meningitis (Meningococcic), *J. A. M. A.* **115**:1091-1095 (Sept. 28) 1940.

36. Hoyne, A. L.: Epidemic Meningitis, *J. A. M. A.* **115**:1852-1855 (Nov. 30) 1940.

37. Bierman, W., and Baehr, G.: The Use of Physically Induced Pyrexia and Chemotherapy in the Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* **116**:292-294 (Jan. 25) 1941.

38. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccine, *New York State J. Med.* **41**:45-50 (Jan. 1) 1941.

and Bierman,³⁹ about 3 per cent of patients recover spontaneously, and of 200 patients treated with sulfanilamide compounds, 6 per cent recovered. Too few patients were treated with other agents to permit determination of percentages. If the infection is localized at the site of a patent ductus arteriosus, another mode of attack, which seems more logical but which obviously can be applied only in special instances, is ligation or excision. Four patients with such a condition were treated by Touroff and Vesell,⁴⁰ with 1 recovery, which had lasted nineteen weeks at the time their report was prepared. We have observed a similar recovery.

Isolated reports of recovery after the use of sulfanilamide or a derivative have appeared, but almost an equal number of failures have been recorded.

One instance of successful treatment of acute ulcerative endocarditis caused by the hemolytic streptococcus with sulfanilamide was reported.⁴¹ My associates and I have had one failure.

Hemolytic Streptococcal Infection.—Opinion is still divided concerning the use of sulfanilamide in treatment of scarlet fever. At a panel discussion at the meeting of the American College of Physicians in Boston, some physicians expressed the belief that chemotherapy had a pronounced effect in reducing complications in cases of hemolytic streptococcal infection, but others were doubtful.

Wesselhoef⁴² advises chemotherapy for any desperate, fulminating, highly toxic infection of the faucial space and trachea probably caused by *Streptococcus haemolyticus*, but is rightly opposed to the indiscriminate use of sulfanilamide compounds in treating minor infections of the respiratory tract. The drugs are of most value in management of sequels of infections, in which the bacteria have invaded the blood, the meninges or the lungs.

In a brief report devoid of details, Lawrence and Sutliff⁴³ claim good results in 10 cases of pneumonia caused by *Str. haemolyticus* treated with adequate amounts of sulfanilamide. In a report of another series of

39. Lichtman, S. S., and Bierman, W.: The Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* **116**:286-289 (Jan. 25) 1941.

40. Touroff, A. S. W., and Vesell, H.: Experiences in the Surgical Treatment of Subacute *Streptococcus Viridans* Endarteritis Complicating Patent Ductus Arteriosus, *J. Thoracic Surg.* **10**:59-83 (Oct.) 1940.

41. Alexander, S., and Alexander, S. F.: Cure of a Case of Ulcerative Endocarditis, *J. A. M. A.* **115**:1712-1713 (Nov. 16) 1940.

42. Wesselhoef, C.: Sulfanilamide in the Management of Acute Streptococcal, Particularly Scarlatinal, Infections of the Upper Respiratory Tract, *New England J. Med.* **224**:221-226 (Feb. 6) 1941.

43. Lawrence, E. A., and Sutliff, W. D.: Streptococcal Pneumonia, *New York State J. Med.* **40**:1233-1275 (Aug. 15) 1940.

more carefully studied cases Keefer and his aids⁴⁴ concluded that, although sulfanilamide reduced the mortality rate both of pneumonia caused by the hemolytic streptococcus and of empyema, the effects were not striking.

Staphylococcic Infection.—More evidence has been accumulated in the past year that sulfathiazole is of value in the treatment of staphylococcic infection, especially with bacteremia, if surgical treatment can control or eliminate the primary or secondary foci. Spink and his associates⁴⁵ report 22 recoveries in 29 cases of bacteremia; Rammelkamp and Keefer,⁴⁶ 3 recoveries in 7 cases. In treating bacteremia, Herrell and Brown⁴⁷ recommend that the level of sulfathiazole in the blood be kept at 16 to 20 mg. per hundred cubic centimeters. They show how adequate treatment with sulfanilamide and its derivatives now gives a patient with bacteremia seven out of ten chances for recovery, instead of the same chances for death, as in the past.

Two patients with staphylococcic meningitis recovered after treatment with sulfathiazole.⁴⁸ Local applications of sulfathiazole seem to be of benefit in the treatment of wounds infected with staphylococci.⁴⁹

Gonococcic Infection.—Kendell and associates⁵⁰ recommend the use of artificially induced pyrexia, together with chemotherapy, in the treatment of gonococcic infection otherwise resistant to sulfanilamide compounds.

Bacillary Infection.—The value of chemotherapy in brucellosis is still unknown. Although Horn,⁵¹ in reviewing 83 cases, concluded that

44. Keefer, C. S.; Rantz, S. A., and Rammelkamp, C. H.: Hemolytic Streptococcal Pneumonia and Empyema: A Study of Fifty-Five Cases with Special Reference to Treatment, *Ann. Int. Med.* **14**:1533-1550 (March) 1940.

45. Spink, W. W.; Hansen, A. E., and Paine, J. R.: Staphylococcic Bacteremia: Treatment with Sulfapyridine and Sulfathiazole, *Arch. Int. Med.* **67**:25-35 (Jan.) 1941.

46. Rammelkamp, C. H., and Keefer, C. S.: Sulfathiazole Therapy of Staphylococcus Aureus Bacteremia, *New England J. Med.* **223**:877-884 (Nov. 28) 1940.

47. Herrell, W. E., and Brown, A. E.: The Treatment of Septicemia, *J. A. M. A.* **116**:179-183 (Jan. 18) 1941.

48. Sadusk, J. F., and Nielsen, A. E.: Use of Sulfathiazole in Staphylococcic Meningitis with Recovery, *J. A. M. A.* **116**:298-300 (Jan. 25) 1941. Dietel, F. W., and Kaiser, A. D.: Staphylococcus Aureus Meningitis Successfully Treated with Sulfathiazole, *ibid.* **115**:601 (Aug. 24) 1940.

49. Spink, W. W., and Paine, J. R.: Local Use of Sulfathiazole in the Treatment of Staphylococcic Infections: Preliminary Report, *Minnesota Med.* **23**:615-618 (Sept.) 1940.

50. Kendell, H. W.; Rose, D. L., and Simpson, W. M.: Combined Artificial Fever-Chemotherapy in Gonococcic Infections Resistant to Chemotherapy, *J. A. M. A.* **116**:357-363 (Feb. 1) 1941.

51. Horn, W. S.: Sulfanilamide in the Treatment of Undulant Fever, *Texas State J. Med.* **36**:232-237 (July) 1940.

sulfanilamide is helpful, such conclusions are subject to doubt, considering the tendency to spontaneous relapses in the disease. Simpson expressed pessimism in regard to chemotherapy brucellosis at the Boston meeting of the American College of Physicians. One group of investigators state that sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methylthiazole) was effective in inhibiting the growth of brucellas in vitro.⁵² According to others,⁵³ sulfamethylthiazole was also effective in treating mice infected with brucellas. In studies on guinea pigs, King and Lucas⁵⁴ demonstrated the curative value of large doses of sulfapyridine, especially in infection caused by *Brucella suis* and less so in that caused by *Brucella abortus*. In vitro tests also showed the destructive effect of the drug on the bacilli. Again *B. abortus* was most resistant.

Neal and her associates⁵⁵ report 14 recoveries among 29 cases of meningitis caused by *Haemophilus influenzae* in which treatment was with sulfapyridine. A specific serum was also used, but the chief benefit was derived from the drug.

Miscellaneous Infections.—In 8 cases of actinomycosis there was apparently good response to therapy with sulfanilamide compounds. British workers⁵⁶ report 5 cases of abdominal actinomycosis, with 4 recoveries. Sulfanilamide and sulfapyridine were used. Dobson and his associates⁵⁶ mention the apparent value of sulfanilamide in this disease and report 3 cases in which beneficial effect seemed to be obtained.

Thomas, France and Reichsman⁵⁷ report the results of a four year study to determine the influence of sulfanilamide in preventing recurrences of rheumatic fever. Results of previous studies had already indicated its possible value, but the period of observation had not been long enough. It now appears that small doses (1.2 Gm. daily) of sulfanilamide given continuously from November to June to patients with a recent history of rheumatic fever were effective. Among 55 patients so treated there were no major recurrences of rheumatic fever or attacks of hemolytic streptococcic infection, while among 67 control patients with a

52. Kempner, W.; Wise, B., and Schlayer, C.: Manometric Determinations of the Effects of Various Sulfonamide Compounds on *Brucella Melitensis*, *Am. J. M. Sc.* **200**:484-492 (Oct.) 1940.

53. Morales-Otero, P., and Pomales-Lebrón, A.: Effects of Sulfanilamide and Sulfamethylthiazole on Experimental *Brucella* (Var. *Melitensis*) Infection in Mice, *Proc. Soc. Exper. Biol. & Med.* **45**:512-515 (Oct.) 1940.

54. King, E. S., and Lucas, M.: Sulfapyridine in Experimental Brucellosis, *J. Lab. & Clin. Med.* **26**:616-620 (Jan.) 1941.

55. Dorling, G. C., and Eckhoff, N. L.: Chemotherapy of Abdominal Actinomycosis, *Lancet* **2**:707-708 (Dec. 7) 1940.

56. Dobson, L.; Holman, E., and Cutting, W.: Sulfanilamide in the Therapy of Actinomycosis, *J. A. M. A.* **116**:272-275 (Jan. 25) 1941.

57. Thomas, C. B.; France, R., and Reichsman, F.: Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *J. A. M. A.* **116**:551-560 (Feb. 15) 1941.

similar history there were 15 major attacks of rheumatic fever, 1 attack of hemolytic streptococcic infection and 1 case of subacute bacterial endocarditis. One patient treated in the winter months had a recrudescence, of rheumatic fever in August, when he was not receiving the drug. No serious toxic effects were noted during the period of prolonged treatment.

ACUTE INFECTIONS OF THE RESPIRATORY TRACT

Influenzal Infection.—Because of the widespread nature of infections of the respiratory tract and of the enormous economic loss entailed each year, numerous recent advances in knowledge concerning them are of importance. Ample evidence now shows that different infectious agents, all filtrable viruses, cause diseases of the respiratory tract which are clinically indistinguishable from one another. This similarity occurs with other diseases, such as lobar pneumonia, which may be caused by pneumococci of various types and yet give a uniform clinical picture. These infections in general are called influenza, grip or cold and usually occur in epidemics, but may be sporadic.⁵³ They set up an inflammatory reaction in the mucous membrane lining the respiratory tract. In the mildest forms only the uppermost portion of the tract is affected, as in rhinitis or nasopharyngitis. Usually, but not always, the severity of the disease and the constitutional symptoms increase as the infection descends progressively, as in pharyngitis, laryngitis, tracheitis, bronchitis, bronchiolitis and, finally, pneumonitis. When all areas are involved the cumbersome term nasopharyngotracheobronchopneumonitis may be applied, but any combination of areas may be affected at a given time or in succession. In a few cases only the lungs seem to be affected. Several important points should be noted: First, pulmonary involvement need not be looked on as a separate disease—pneumonia—but should be regarded rather as a part, or as the severe form, of common widespread mild infection. Second, infection caused by a filtrable virus may, under certain circumstances, prepare the way for the invasion of pathogenic bacteria which may cause a fatal form of pneumonia. This relation has been recognized for years, but the first proved cases were reported by Stokes and Wolman^{52a} and also by Finland, who described them at the meeting of the Association of American Physicians in May 1941. In both instances influenza was followed by fulminating staphylococcic pneumonia. Curiously, bacterial pneumonia, for some unknown reason, has not been a serious problem in epidemics of recent years, as it was in the

53. Scupham, G. W.: The Therapy of Influenza, *J. A. M. A.* **116**:2264-2268 (May 17) 1941.

52a. Stokes, J., Jr., and Wolman, I. J.: The Probable Synergism of Human Influenza Virus and *Staphylococcus Aureus* in a Rapidly Fatal Respiratory Infection, *Internat. Clin.* **1**:115-122 (March) 1940.

pandemic of "influenza" in 1918-1919. Third, sulfanilamide compounds have no effect on patients with such infection. The drugs should not be used unless invasion by bacteria known to be amenable to chemotherapy is evident or is threatened.

The problem for the present is to discover the etiologic agents of those infections not caused by the virus of influenza and to bring them into relation with each other. Progress has already been made. Almost simultaneously five "new" viruses isolated from patients in different parts of the country are reported by Magill⁵⁹ (TM virus), Francis⁶⁰ (influenza virus B), Weir and Horsfall⁶¹ (virus virulent for mongooses), Dyer and associates and Lillie and associates⁶² (Q fever virus) and Eaton⁶³ (psittacosis-like virus). Two of the viruses⁶⁴ are somewhat similar to the influenza virus A of Smith, Andrewes and Laidlaw; one⁶² is related to the virus of Australian Q fever; one⁶³ is a psittacosis-like virus, and the last⁶¹ is apparently a new virus. It is important to learn if any of these viruses were operative in the nation-wide epidemic of disease of the respiratory tract in December 1940 and January 1941.

At present two varieties of influenza are recognized, influenza A, caused by the virus first isolated by Smith, Andrewes and Laidlaw,⁶⁵ and a similar infection caused by influenza virus B, described by Francis.⁶⁰ The B virus isolated by Francis was serologically distinct from the A virus and could be easily distinguished from it by the complement fixation test.⁶⁶ Because of clinical and epidemiologic similarities between influenza A and other forms of influenza, American

59. Magill, T. P.: A Virus from Cases of Influenza-Like Upper Respiratory Infection, *Proc. Soc. Exper. Biol. & Med.* **45**:162-164 (Oct.) 1940.

60. Francis, T.: A New Type of Virus from Epidemic Influenza, *Science* **92**: 405-408 (Nov. 1) 1940.

61. Weir, J. M., and Horsfall, F. L.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, *J. Exper. Med.* **72**: 595-610 (Nov.) 1940.

62. Dyer, R. E.; Topping, N. H., and Bengtson, I. A.: An Institutional Outbreak of Pneumonitis: II. Isolation and Identification of Causative Agent, *Pub. Health Rep.* **55**:1945-1954 (Oct. 25) 1940. Lillie, R. D.; Perrin, T. L., and Armstrong, C.: An Institutional Outbreak of Pneumonitis: III. Histopathology in Man and Rhesus Monkeys in the Pneumonitis Due to the Virus of "Q" Fever, *ibid.* **56**:149-155 (Jan. 24) 1941.

63. Eaton, M. D.; Beck, D., and Pearson, H. E.: Isolation of a Virus from Four Cases of Atypical Pneumonia by Intranasal Inoculation of Mice, *J. Bact.* **41**: 58-59 (Jan.) 1941; A Virus from Cases of Atypical Pneumonia: Relation to Viruses of Meningopneumonitis and Psittacosis, *J. Exper. Med.* **73**:641-653 (May) 1941.

64. Magill.⁵⁹ Francis.⁶⁰

65. Smith, W.; Andrewes, C. H., and Laidlaw, P. P., cited by Horsfall, F. L.: Present Status of Knowledge of Influenza, *Am. J. Pub. Health* **30**:1302-1310 (Nov.) 1940.

66. Francis, T.: Differentiation of Influenza A and Influenza B by the Complement-Fixation Reaction, *Proc. Soc. Exper. Biol. & Med.* **45**:861-863 (Dec.) 1940.

investigators at the Rockefeller Institute and British workers at the National Institute for Medical Research in London suggest that all forms be regarded as influenza.⁶⁷ Viruses similar to the influenza A and B viruses which are subsequently isolated may perhaps be identified as the C virus, the D virus, and so forth. It is wise, as the authors suggest, to submit different and newly isolated strains of viruses to either institute for approval before naming, in order to avoid confusion and to establish uniformity in nomenclature. Possibly some of the five new varieties mentioned previously may fit into this scheme of classification; some may be identical, and some may be so different as to warrant other terminology—for example the virus virulent for mongooses,⁶¹ the Q fever virus⁶² and psitticosis-like virus.⁶³

According to the views Horsfall expressed at the Boston meeting of the American College of Physicians, results of serologic studies on the serum from different groups of patients suggest that at least three kinds of influenza, or influenza-like disease, were prevalent during the winter of 1940-1941. One was influenza A, another influenza B and another a form which was neither A nor B and which may have been caused by one or more viruses other than the A and B types. Magill and Tyndall⁶⁸ show that patients may have repeated attacks of influenza, each attack caused by a different type of virus, yet the diseases may be clinically indistinguishable.

Influenza A: One large rural community was studied over a two year period. Neutralizing antibodies against influenza A virus were present at the highest titer in adolescent persons and were constant, but they were independent of a history of clinical influenza. Among 59 persons who subsequently contracted influenza, it was found that susceptibility to infection and a low titer of neutralizing antibodies were correlated, but a high titer did not guarantee immunity. After the epidemic, an increase in antibodies in the blood of many persons who had not been sick indicated that they had had subclinical infections.

Influenza B: A clinical description of a form of influenza in cases of which Francis isolated influenza B virus is reported.⁶⁹ The outbreak occurred in a hospital for rheumatic children in February and March

67. Horsfall, F. L.; Lennette, E. H.; Rickard, E. R.; Andrewes, C. H.; Smith, W., and Stuart-Harris, C. H.: The Nomenclature of Influenza, *Lancet* **2**:413-414 (Oct. 5) 1940.

68. Magill, T. P.: Repeated Attacks of Influenza, *Proc. Soc. Exper. Biol. & Med.* **46**:316-318 (Feb.) 1941. Magill, T. P., and Tyndall, M.: Two Outbreaks of Influenza Caused by Antigenically Different Viruses, *ibid.* **46**:371-374 (March) 1941.

69. Reyersbach, G.; Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis: Clinical and Epidemiological Observations, *J. Clin. Investigation* **20**:289-294 (May) 1941.

1940. Fifty of 108 children (46 per cent) contracted the disease during thirty-one days, regardless of whether large doses of vitamin were given.⁷⁰ None of the 40 adults in attendance was infected. The most common symptoms were headache, drowsiness and slight malaise. Thirteen children had no symptoms at all. Coryza and slight cough were present in 10. Involvement of the upper respiratory tract was surprisingly absent. Leukopenia, as in our experience, was the most important single test for differentiating cases of influenza from cases of pharyngitis caused by hemolytic streptococci which occurred at the same time. Nothing suggested that the influenza virus helped the spread of hemolytic streptococci or increased their invasiveness, nor did the disease cause recurrences of rheumatic fever.

Miscellaneous Studies: Taylor⁷¹ suggests that the cells of pulmonary tissue serve as a haven, as well as a trap, for the virus of influenza. The virus apparently increases intracellularly and can be neutralized by antibody only if it escapes. As long as the virus is retained within cells it multiplies. If the cells are disrupted the augmented virus, unless neutralized, spreads and invades other cells. Thus it appears that the virus paves the way for bacterial invasion, and once the bacteria are operative they may disrupt the cells, liberating more free virus, which in turn spreads farther. Such a hypothesis may account for the similarity of cases of what is commonly called influenza pneumonia, regardless of the kind of superinvading bacteria (see the discussion on staphylococcic pneumonia, page 348).

According to Chambers and Henle,⁷² particles sedimented from Berkefeld filtrates of emulsified lungs of mice with influenza are the same, except for their infectious property, as particles from lungs of normal mice. Some component of normal lung, therefore, acquires infectivity by a structural rearrangement or by adsorption of an infectious agent of much smaller size. The carrier function of the cell constituents is further suggested by the fact that antiserum against particles from normal mouse lung causes clumping of infected preparations.

Francis and Moore⁷³ confirmed previous work showing that some strains of influenza virus may be induced to become neurotropic. This

70. Kuttner, A. G.: The Effect of Large Doses of Vitamin A, B, C and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children, *ibid.* **19**:809-812 (Nov.) 1940.

71. Taylor, R. M.: Experimental Infections with Influenza A Virus in Mice: The Increase in Intrapulmonary Virus After Inoculation and the Influence of Various Factors Thereon, *J. Exper. Med.* **73**:43-55 (Jan.) 1941.

72. Chambers, L. A., and Henle, W.: A Study of the Relationship Between the Virus of Influenza A and Filtrable Components of Normal Lungs, read at the meeting of the American Society for Experimental Pathology, Chicago, April 17, 1941; abstracted in program, p. 6.

73. Francis, T., and Moore, A. E.: A Study of the Neurotropic Tendency in Strains of the Virus of Epidemic Influenza, *J. Exper. Med.* **72**:717-728 (Dec.) 1940.

fact may aid in explaining the occasional occurrence of encephalitis during epidemics of influenza.

Horsfall and Lennette ⁷⁴ report further observations on the complex influenza-distemper vaccine discussed in last year's review.^{74a} The vaccine, for some unknown reason, is multivalent and immunizes human volunteers against a number of different strains of influenza virus. Tests are under way this season to determine the effect of the vaccine in preventing the prevalent infections of the respiratory tract. In two studies already reported ^{74b} the effects of the vaccine in preventing influenza or in ameliorating the symptoms were not striking.

A Russian investigator ⁷⁵ reports success in "vaccine treatment" of patients with influenza. He induces them to inhale virus vaccine in the form of a mist in the first few days of the disease itself. His conclusions are not convincing. Vaccine of any kind used therapeutically has never been proved efficacious in a specific sense.

Burnet and Foley ⁷⁶ record success in isolating the virus of influenza from patients by inoculating filtered washings into the amniotic cavity of chick embryos. They hope that by such a technic it may also be possible to isolate viruses other than those of influenza and suggest that this medium can be used in the production of anti-influenza vaccine.

Acute Pulmonary Infections.—Often when a successful treatment of a certain disease or group of diseases is discovered, as in the use of sulfanilamide and its derivatives in cases of pneumonia, many problems seem settled and interest is focused on new ones. The increased attention recently devoted to those forms of pneumonia not influenced by therapy with these drugs has led to the discovery of a surprising variety of acute pulmonary infections.

For several years there have been sporadic reports by Gallagher, Brown, Allen, Cass, Bock, Scadding and others of a mild atypical form of pneumonia or pneumonitis. The disease usually occurred during an epidemic of mild infection of the respiratory tract and in most cases was considered to be influenza. In none of the reports was it suggested

74. Horsfall, F. L., and Lennette, E. H.: Synergism of Human Influenza and Canine Distemper Viruses in Ferrets, *J. Exper. Med.* **72**:247-259 (Sept.) 1940.

74a. Reimann, H. A.: Infectious Diseases, *Arch. Int. Med.* **66**:478-525 (Aug.) 1940.

74b. Dalldorf, G.; Whitney, E., and Ruskin, A.: A Controlled Test of Influenza A Vaccine, *J. A. M. A.* **116**:2574-2577 (June 7) 1941. Martin, W. P., and Eaton, M. D.: Experiments on Immunization of Human Beings Against Influenza A, *Proc. Soc. Exper. Biol. & Med.* **47**:405-409 (June) 1941.

75. Nechaev, A. V.: Effectiveness of Specific Virus Vaccine Therapy in Grip by Inhalation, *Sovet. med.* (no. 7) **4**:25-29, 1940.

76. Burnet, F. M., and Foley, M.: Two Methods for the Detection of Influenza Virus in Human Throat Washings Without the Use of Ferrets, *M. J. Australia* **1**:68-72 (Jan. 18) 1941.

that the disease might be a still unrecognized one, apart from specific influenza, and no attempt was made to discover the etiologic agent.

In 1938, after studying a series of 8 cases of a peculiar severe pulmonary infection, I pointed out that it might represent a newly recognized disease entity, probably caused by a filtrable virus without the agency of bacteria and, with the aid of others, proved that it was not caused by the virus of influenza. In 1940 Havens and I⁷⁷ reported a large epidemic of infections of the respiratory tract occurring in 1939, in which were a few cases of pneumonitis similar in many respects to the cases of severe infection studied the previous year. At the time we regarded the two diseases as identical, but we might have been mistaken. In the fall, winter and spring of 1940 and 1941 we again observed 9 cases of severe pulmonary infection like those of 1938, and, as before, psittacosis was suspected in 3 cases. In 1 case the termination was fatal and necropsy was performed. Bacteria-free pneumonia with an exudate of polymorphonuclear cells was present. The 9 cases were isolated and sporadic, occurred mostly in persons over 35 and, like those reported by Smiley and his associates, by Kneeland and Smetana, by Longcope and by Gallagher,^{77a} were not associated with large numbers of cases of mild, nonpneumonic diseases. Most of the other reported cases of pneumonitis, like ours of 1939, occurred during widespread epidemics, usually in the winter months. It is therefore possible, or probable, that the severe, sporadic, nonseasonal infections with a relatively long incubation period comprise an entity distinct from the epidemic forms. The question can be settled by the discovery of the etiologic agents.

Pulmonary diseases similar to the one I reported in 1938 are described under the titles "Current Bronchopneumonia"⁷⁸ and "Bronchopneumonia of Unknown Etiology."⁷⁹ These two reports, which include the first necropsy data, confirm the prediction that the pneumonia is of a peculiar kind, characterized by inflammation of the pulmonary stroma and by a bacteria-free exudate composed of mononuclear cells. The only deaths thus far reported were those of patients with other serious diseases as well. The authors noted no favorable effect from treatment with sulfanilamide and its derivatives and were unable to determine the causative agent. Pneumococci were notably scarce.

77. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, *Arch. Int. Med.* **65**:138-150 (Jan.) 1940.

77a. Gallagher, J. R.: Acute Pneumonitis: A Report of Eighty-Seven Cases Among Adolescents, *Yale J. Biol. & Med.* **13**:663-678 (May) 1941.

78. Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, *Bull. Johns Hopkins Hosp.* **67**:229-267 (Oct.) 1940.

79. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X), *Bull. Johns Hopkins Hosp.* **67**:268-305 (Oct.) 1940.

Although I surmised that the disease I described in 1938 was caused by a filtrable virus, the first substantial support for this view comes from the work of Weir and Horsfall,⁶¹ who isolated a new virus from patients with similar disease. The virus was not pathogenic for the animals generally used in the laboratory but caused pulmonary disease in wild mongooses tested in Jamaica. The fact that the virus was specifically neutralized by serum from mongooses and from patients convalescent from the disease is evidence that it was the causative agent. Samples of convalescent serum from many of the patients included in our reports were sent to Drs. F. L. Horsfall, T. Francis, T. P. Magill, K. Meyer, J. Stokes and H. R. Cox, who tested them. No antibodies against the virus of influenza A, influenza B, American Q fever or psittacosis were present. Evidence at hand therefore suggests that the infection I and others have described represents one or more etiologic entities. References to many published clinical reports may be found in another paper.⁷⁷

American Q Fever: Members of the National Institute of Health⁶² report a localized outbreak of a peculiar disease, with associated pneumonitis, in Washington, D. C. It occurred among workers in a building where research on Q fever was in progress, but no person actually working with the virus was infected. The clinical similarity of the infection to that of virus pneumonia, described under the previous heading, was striking, but it was found to be caused by the rickettsia of Q fever. American Q fever is supposedly identical with Australian Q fever, but clinical reports of the latter disease mention little or nothing about involvement of the respiratory tract. On the other hand, in the Washington outbreak the symptoms localized in the respiratory tract were not prominent, and the pulmonary lesions were discovered mainly by roentgenographic examination. It is possible that similar lesions might have been observed in cases of the Australian form had roentgenograms been made routinely.

Histologic changes in the lung in a case of fatal Q fever were remarkably similar to those reported by Kneeland and Smetana and by Longcope in cases of probable virus infection of the lungs.

Hesdorfer and Duffalo⁸⁰ report a probable case of Q fever, possibly contracted in a forest in Montana in December. No evidence of the bite of a tick or other insect was present. The clinical course of the disease, except for the development of leukocytosis, resembled that of the outbreak in Washington. The authors cite another case in Montana, occurring in the late fall of 1939, in which *Rickettsia diaporica* was isolated. These cases further suggest that Q fever may at times be encountered outside of

80. Hesdorffer, M. B., and Duffalo, J. A.: American Q Fever, *J. A. M. A.* **116**:1901-1902 (April 26) 1941.

the laboratory, but it probably has no relation to the widespread "virus" pneumonia reported by others.

Miscellaneous Infections: Eaton ⁶³ described a disease of the respiratory tract apparently caused by a psittacosis-like virus. The virus seemed to be identical with the virus of meningoencephalitis of Francis and of Magill, which the latter thought to be of animal origin. Pinkerton and associates,⁸¹ however, believe that the virus is closely related to, if not identical with, a psittacosis-like one they obtained from pigeons. All three, they believe, may be modified psittacosis viruses or different types of psittacosis virus.

After studying an epidemic of 32 cases, Adams ⁸² described a new form of primary "virus" pneumonitis in infants, differing from the secondary form previously described by Goodpasture. Nine infants died. No adults contracted the infection. Important symptoms included cough, dyspnea, cyanosis, roentgenographic evidence of pneumonia and low grade fever, which was often biphasic. Cytoplasmic inclusions characteristic of virus infection were present in the epithelial cells of the bronchial tree in all cases which terminated fatally and in the alveolar cells in 5 cases.

Pinkerton and Henderson,⁸³ in describing toxoplasmosis in adults (page 362), report a resemblance of the pulmonary reaction to that of virus pneumonia. In some respects the clinical picture was similar. Yet there is little likelihood of any relation between the two diseases.

Armstrong and Hornibrook ⁸⁴ report a case of lymphocytic choriomeningitis which had been regarded as one of influenza because neurologic symptoms were not present. Because in their previous studies about 11 per cent of 2,000 samples of serum collected at random contained antibodies for the virus, the authors suggest that some cases of disease resembling influenza and diagnosed as such may actually have been cases of lymphocytic choriomeningitis, without nervous symptoms.

In summary, the following diseases and infectious agents may be listed as specific entities or as causes of acute disease of the respiratory

81. (a) Pinkerton, H., and Moragues, V.: Comparative Study of Meningo-Pneumonitis Virus and Modified Psittacosis Enzootic in Pigeons, to be published. (b) Pinkerton, H., and Swank, R. L.: Recovery of Virus Morphologically Identical with Psittacosis from Thiamin-Deficient Pigeons, *Proc. Soc. Exper. Biol. & Med.* **45**:704-706 (Nov.) 1940.

82. Adams, J. M.: Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies: Study of an Epidemic Involving Thirty-Two Infants, with Nine Deaths, *J. A. M. A.* **116**:925-933 (March 8) 1941.

83. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, *J. A. M. A.* **116**:807-814 (March 1) 1941.

84. Armstrong, C., and Hornibrook, J. W.: Choriomeningitis Virus Infection Without Central Nervous System Manifestations, *Pub. Health Rep.* **56**:907-909 (April 25) 1941.

tract or of atypical forms of pneumonia, nearly all discovered within the past few years; virus pneumonia, American Q fever, coccidioidomycosis,⁸⁵ virus pneumonitis, lymphocytic choriomeningitis, toxoplasmosis, T. M. virus, influenza A virus, influenza B virus, virus virulent for mongooses and a psittacosis-like virus.

Vaccines for Infections of the Respiratory Tract.—Walsh,⁸⁶ although he admits the uselessness of cold vaccines given orally or parenterally, suggests that a vaccine composed of the usual gamut of germs be applied directly into the nares with an atomizer. This, he claims, is a logical procedure which results in the establishment of local immunity. Further studies by Diehl and Baker⁸⁷ reveal no evidence that heat-killed vaccines have any value in the prevention of colds.

PNEUMONIA

The chemotherapy of pneumonia has been discussed in the section entitled "Chemotherapy of Coccid Diseases."

From all indications, there has been a further decline in the mortality rate from pneumonia, so that, according to recent statistics,⁸⁸ the disease is the fifth most important cause of death, instead of the second or third. There is no doubt that the recent decline in mortality, particularly that from pneumococcic pneumonia, is in a large part due to the successful use of chemotherapy. But, as I pointed out in last year's review,⁸⁹ other causes unrelated to chemotherapy are operative as well. It is well known that pneumonia in general varies from year to year, from season to season and from place to place. The variation is due not to a change in any single disease entity, but to a change in the etiologic kinds of pneumonia prevalent. In my own experience, for example, cases of typical pneumococcic lobar pneumonia were much less frequent in the winter of 1941 than in previous years. In only one third of the cases was the pneumonia regarded as typical. The rest were classified as representing atypical forms of varied etiologic nature, among which were 9 cases of the peculiar form called, for convenience, virus pneumonia. In 3 of these cases psittacosis was suspected, but was ruled out by the results of appropriate tests. In the 1 case with fatal termination which was studied post mortem, the exudate in the lungs was not like that reported by Kneeland or Longcope,

85. Farness, O. J.: Coccidioidomycosis, J. A. M. A. **116**:1749-1752 (April 19) 1941.

86. Walsh, T. E.: Intranasal Vaccine Spray: Its Use in Prophylaxis Against the Common Cold, Ann. Otol., Rhin. & Laryng. **49**:875-894 (Dec.) 1940.

87. Diehl, H. S., and Baker, A. B.: Cold Vaccines: A Further Evaluation, J. A. M. A. **115**:593-594 (Aug. 24) 1940.

88. Excellent Health Record for 1940, Statist. Bull. Metrop. Life Ins. Co. **22**: 1-7 (Jan.) 1941; Pneumonia Control: Another Public Health Triumph, *ibid.* **22**: 7-10 (March) 1941.

89. Reimann, H. A.: Infectious Diseases, Arch. Int. Med. **66**:478-525 (Aug.) 1940.

but was composed of polymorphonuclear cells. No bacteria were found either in cultures or in stained sections. In no case was a virus isolated and serologic studies, made by Drs. F. L. Horsfall, H. R. Cox, T. Francis and J. Stokes, showed no evidence of infection with viruses already known. Treatment with sulfanilamide compounds had no effect.

Somewhat similar experiences are reported by others in different parts of the country, for example, by Bracken,⁹⁰ in Pittsburgh, where since 1939 cases of pneumonia apparently caused by "mixed infection" predominated over those of pneumococcic form, and by Gallagher.^{77a} In an attempt to make an etiologic diagnosis, care should be taken not to incriminate bacteria simply because of their habitual presence in the throat. Pneumococci of the higher numbered types, not including types V, VII, VIII or XIV, as well as *Streptococcus viridans*, are commonly present in normal throats and may have nothing to do with an associated pneumonia. An error was apparently made by two investigators⁹¹ who diagnosed the condition in several cases as pneumonia caused by *Str. viridans* simply because these bacteria were present in the sputum and because sulfapyridine therapy failed. One patient received 74 Gm. of the drug (1,140 grains) and died!

A short, but valuable, paper by Faller, Quickel and Smith⁹² shows how unreliable are statistics gathered from large numbers of reports. As a sampling method they reviewed the hospital records of 131 patients whose deaths were ascribed to pneumonia. After careful scrutiny of the data they concluded that only 75 of the patients actually died of pneumonia and that in 21 pneumonia was definitely not the cause of death. How much, then, can one rely on statistics concerning thousands of cases collected by various students of pneumonia control?

Pneumococcic Pneumonia.—Kaufmann and his associates,⁹³ in Denmark, add 20 new types to the 32 types of pneumococci. This is more of academic than of practical importance at present, since many of the new types are but subtypes of ones now recognized. For example, only types XXXIII, XXXIV, XXXV, XXXVII and XXXVIII are not related to the others, but type VII is apparently composed of types VII, VII A, VII B and VII C. The authors show that many of Cooper's types have such subtypes and that serum prepared with one may not be wholly effective against a related one. These finer differential serologic

90. Bracken, M. M.: Some Bacteriologic Observations on Pneumonia, *Am. J. M. Sc.* **201**:340-347 (March) 1941.

91. Senerchia, F. F., and Livengood, H. R.: *Streptococcus Viridans Pneumonia*, *New York State J. Med.* **41**:143-145 (Jan. 15) 1941.

92. Faller, C.; Quickel, K. E., and Smith, C. W.: Pneumonia Deaths and Deaths Ascribed to Pneumonia: A Critical Study of One Hundred and Thirty-One Deaths Ascribed to Pneumonia, *Pennsylvania M. J.* **44**:563-567 (Feb.) 1941.

93. Kaufmann, F.; Mørch, E., and Schmith, K.: On the Serology of the Pneumococcus-Group, *J. Immunol.* **39**:397-426 (Nov.) 1940.

factors are not reflected in tests made in the usual way. In Finland's ⁹⁴ recent study, for example, less than 1 per cent of strains of pneumococci encountered in a large group of persons failed to react with serum for types I to XXXII. A similar percentage was reported by Gundel several years ago.

Results of experimental studies by Hamburger and Robertson ⁹⁵ on the dog show how important the viscosity of edema fluid or exudate is in the spread of pneumonia from one place to another. The more fluid the exudate, the greater its penetration to the depths of the lung and the less effective its elimination through the trachea. In the spread of pneumonia, much depends on gravity as well.

In studies on the mechanism of recovery from pneumonia, Wood ⁹⁶ supports views expressed by Loeschcke. Pneumococci are carried from place to place in edema fluid, and few are present in the alveoli. The spread is greatly enhanced by the edema-producing substance described by Sutliff. His results differed from those of Kempf and Nungester, who were not able to demonstrate the penetration of antipneumococcus immune bodies into the pneumonic lesions after intravenous injection of serum. Serum not only entered the lesion, but did so in amounts large enough to control the spread of infection. Capsular swelling and clumping of pneumococci occurred, even in the larger bronchi. The bacteria apparently became sticky and adhered to adjacent cells. The phenomena undoubtedly aided in checking the spread of infection.

Several groups ⁹⁷ of investigators report outbreaks of type-specific pneumococcic infections in families and in institutions and show again

94. Finland, M.; Brown, J. W., and Barnes, M. W.: Immune Reaction of Carriers and Noncarriers of Type Specific Pneumococci, *Am. J. Hyg. (Sect. B)* **32**:24-37 (Sept.) 1940.

95. Hamburger, M., and Robertson, O. H.: Studies on the Pathogenesis of Experimental Pneumococcus Pneumonia in the Dog: Secondary Pulmonary Lesions; Relation of Bronchial Obstruction and Distribution of Pneumococci to Their Inception, *J. Exper. Med.* **72**:261-274 (Sept.) 1940. Robertson, O. H., and Hamburger, M.: Studies on Pathogenesis of Experimental Pneumococcus Pneumonia in the Dog: Secondary Pulmonary Lesions; Their Production by Intratracheal and Intrabronchial Injections of Fluid Pneumonic Exudate, *ibid.* **72**:275-288 (Sept.) 1940.

96. Wood, W. B.: Studies on the Mechanism of Recovery in Pneumococcal Pneumonia: I. Action of Type Specific Antibody upon the Pulmonary Lesion of Experimental Pneumonia, *J. Exper. Med.* **73**:201-222 (Feb.) 1941.

97. Smillie, W. G., and Jewett, O. F.: The Relationship of Immediate Family Contact to the Transmission of Type Specific Pneumococci, *Am. J. Hyg. (Sect. A)* **32**:79-88 (Nov.) 1940. Plummer, N., and Ensworth, H. K.: A Family Outbreak of Pneumococcus Type I Infection, *Am. J. M. Sc.* **201**:100-106 (Jan.) 1941. Dauer, C. C.; Dowling, H. F., and Noble, J. E.: Outbreak of Type II Pneumococcus Pneumonia in an Institution for Children, *Am. J. Hyg. (Sect. A)* **33**:1-8 (Jan.) 1941. Gellis, S. S., and Mitchell, A. G.: Cross Infection with Type I Pneumococcus, *J. A. M. A.* **116**:2580-2581 (June 7) 1941.

that under special circumstances pneumococcic pneumonia is contagious. Other localized pneumococcic disease, such as otitis media, mastoiditis or bronchitis, caused by the same type of pneumococcus may develop in a person in contact with those who have pneumonia.

In Finland's studies ⁹⁴ of carriers and noncarriers of pneumococci, 56 per cent of persons observed carried pneumococci, chiefly of the higher numbered types, as has been found in many previous surveys. It was surprising that certain carriers had, or acquired, homologous type-specific antibodies without evidence of actual infection. Under such circumstances the agglutinin test cannot be used to establish the etiologic cause of pneumonia should it occur. Furthermore, atypical pneumonia, not caused by the pneumococci present in the throat, developed in 4 of the carriers. These observations reemphasize that the mere presence of pneumococci does not mean they are the cause of pneumonia. This fact is important for a physician to bear in mind when deciding whether to employ chemotherapy or serotherapy. Fallor and his associates ⁹² state that it is also an important source of error in the diagnosis of pneumonia.

Frisch ⁹⁸ reports further work on the value of studies of the sputum as an aid in determining the prognosis and as a guide in instituting therapy. The number of pneumococci in the sputum is a reflection of the number of pneumococci in some pneumonic areas of the lung. Patients with many pneumococci in the sputum may require more vigorous therapy. The test is less applicable in cases of type III pneumococcic pneumonia, in which the relation is not so distinct. The amount of capsular substance produced, rather than the number of invading bacteria, determines the outcome of type III pneumococcic pneumonia.

Bigg and Harvey ⁹⁹ report a case of pneumonia in which they claim that four relapses occurring over a period of fifty days were caused by four types of pneumococci. Their evidence is not convincing. The patient first had type II pneumococcic pneumonia, with bacteremia; he recovered after serotherapy, and later urticaria developed. On the fifteenth day of the patient's stay in the hospital pneumonia recurred, and pneumococci of types II, VI and XXIV were found in the sputum. Sulfapyridine produced improvement. Pain in the chest and fever again appeared on the twenty-sixth day, and pneumococci of type XX were found. This time sulfapyridine was ineffectual. There was no indication of a fourth relapse in the data given, and the third, the authors admit, may have been caused by an infarct. Empyema, pulmonary abscess and pneumonia

98. Frisch, A. W.: Sputum Studies in Type III Pneumonia, *Am. J. Clin. Path.* **10**:873-881 (Dec.) 1940.

99. Bigg, E., and Harvey, R. A.: Consecutive Attacks of Pneumococcic Pneumonia: Report of a Case Exhibiting Four Relapses Due to Four *Pneumococcus* Types, *J. A. M. A.* **116**:815-817 (March 1) 1941.

were found post mortem, but the recovery of type XX pneumococci from the lungs is not mentioned. The authors apparently assume too much when they regard the presence of agglutinins for types XX and XXIV as certain evidence that pneumococci of these types actually caused pneumonia. Studies of carriers and noncarriers have shown that homologous type-specific antibodies may develop in a large percentage of healthy constant carriers.¹⁰⁰

McCracken¹⁰¹ describes what he considers to be a case of acute pneumococcic hemorrhagic ulcerative gastroenteritis, an entity which he states is well known in Europe. There is little or no proof that a pneumococcus was the cause, either in the cases he cites or in the one he reports. The condition described may have been the result of some unrecognized disease or of a combination of diseases.

Maclachlan and his associates¹⁰² continue to report studies on therapy with hydroxyethylapocupreine dihydrochloride. The mortality rate of patients whose pneumonia was treated with this drug was, in their experience, about the same as that of patients treated with sulfapyridine. A group of investigators¹⁰³ used roentgen therapy on dogs with pneumococcic pneumonia. Although the authors believe that when a sufficient dose is used there is a "trend" toward survival, as compared with the outcome among untreated dogs, the difference is so little that the results are unconvincing. They do not refer to negative results reported by other authors.

Although pneumococcic pneumonia and pulmonary tuberculosis seldom occur together, cases of the diseases in association were reported.^{103a}

Hemolytic Streptococcic Pneumonia.—Eighty-one cases of this variety of pneumonia are reported in one paper, but the authors⁴² give such meager data that it is doubtful how many were genuine. Empyema occurred in only 3 per cent. The mortality rate was said to be 8 per cent.

100. Finland, M., and Tilghman, R. C.: Bacteriological and Immunological Studies in Families with Pneumococcic Infections: The Development of Type-Specific Antibodies in Healthy Contact Carriers, *J. Clin. Investigation* **15**:501 (Sept.) 1936. Finland, Brown and Barnes.⁹⁴

101. McCracken, J. T.: Enterorrhagia Complicating Lobar Pneumonia: Acute Pneumococcic Hemorrhagic Ulcerative Gastroenteritis with Report of a Case, *Arch. Int. Med.* **67**:36-42 (Jan.) 1941.

102. Maclachlan, W. W. G.; Johnston, J. M.; Bracken, M. M., and Pierce, L. S.: A Comparison of the Mortality in Pneumococcic Pneumonia Treated by Hydroxyethylapocupreine and by Sulfapyridine, *Am. J. M. Sc.* **201**:367-374 (March) 1941.

103. Lieberman, L. M.; Hodes, P. J., and Leopold, S. S.: Roentgen Ray Therapy of Experimental Lobar Pneumonia in Dogs, *Am. J. M. Sc.* **201**:92-100 (Jan.) 1941.

103a. Pedigo, G. W., and Coleman, E. O.: Pneumococcal Pneumonia Complicating Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **43**:258-262 (Feb.) 1941.

After a more detailed study, investigators in Boston ⁴³ report 55 cases, in 16 of which empyema developed. The mortality rate was 17 per cent and increased when there was associated bacteremia. The death rate in those cases in which empyema developed was 18 per cent. Chemotherapy is discussed on page 332.

Staphylococcic Pneumonia.—Stokes and Wolman ¹⁰⁴ observed a case of rapidly fatal staphylococcic pneumonia. Cultures of material from the lungs made at necropsy yielded the virus of epidemic influenza and *Staphylococcus aureus*. Although authors regard the combined infection as a synergistic one, it may be simpler to assume that the virus infection injured the tissue so that staphylococci could become invasive (cf. page 338). The severity of the disease may have been largely due to the powerful toxin which certain strains of staphylococci produce.

At a recent meeting of the Association of American Physicians, Finland reported a number of cases of staphylococcic pneumonia which was apparently induced by influenza. Sporadic or localized epidemics of staphylococcic pneumonia occasionally occur, the largest one, as reported by Chickering, being in 1919. I reported a series of about 10 cases occurring in Minnesota in the winter of 1933, but have seen only an isolated case or two since then. In most of the cases the disease was preceded by an influenza-like infection, but methods for virus studies had not yet been devised at that time. It is interesting to speculate why staphylococcic pneumonia occurs during some epidemics of influenza and not during others, and whether a peculiar strain of influenza virus or peculiar strains of staphylococci are essential to its development.

Friedländer Pneumonia.—Solomon ¹⁰⁵ reports 17 cases of chronic infection of the lung, caused by the Friedländer bacillus, in which the mortality was 23.5 per cent. The condition is often mistaken for pulmonary tuberculosis. Sulfapyridine therapy yielded results sufficiently encouraging to warrant further trial of the drug.

Results of a study of postoperative and post-traumatic pneumonia were published by Stoneburner and Finland.¹⁰⁶ Interference with respiration seemed to be the chief single factor in the cause of pneumonia. Pneumococcic pneumonia, when it did occur, was like that of the primary form but tended to be atypical and to be caused by types of pneumococci often found in healthy carriers.

104. Stokes, J., Jr., and Wolman, I. J.: The Probable Synergism of Human Influenza Virus and *Staphylococcus Aureus* in a Rapidly Fatal Respiratory Infection, *Internat. Clin.* **1**:115-122 (March) 1940.

105. Solomon, S.: Chronic Friedländer Infection of the Lungs, *J. A. M. A.* **115**:1527-1536 (Nov. 2) 1940.

106. Stoneburner, L. T., and Finland, M.: Pneumococcic Pneumonia Complicating Operation and Trauma, *J. A. M. A.* **116**:1497-1504 (April 5) 1941.

Lipid pneumonia has been reviewed by Cannon¹⁰⁷ and pleuropulmonary tularemia by Blackford and Casey.¹⁰⁸

Moolten¹⁰⁹ reports an unusual case of infection and necrosis of the lung associated with diabetes.

Rheumatic Fever.—For years Kuttner and Krumwiede¹¹⁰ closely observed the effect of infection with the hemolytic streptococcus on rheumatic children. Three outbreaks of hemolytic streptococcic infection of the respiratory tract occurred during three successive winters, and the incidence of rheumatic fever after the infection varied greatly. In the first season rheumatic disease recurred in one half of the children; after the second no rheumatic infection appeared, and after the third there were only a few recurrences. Except that the streptococci prevalent in each attack were of different numbered types, there were no significant differences to account for the subsequent variation in rheumatic attacks. At present there is neither an explanation for the differences noted nor any way to predict the outcome. It is highly important to be aware of the great variability in the occurrence, or incidence, of rheumatic fever after hemolytic streptococcic infection. Unless studies are well controlled, the use of any special experimental methods for prophylaxis or treatment may give rise to false conclusions should a spontaneous absence of sequels be ascribed to whatever procedure was used.

Because the outbreaks of streptococcic infection were caused by organisms not previously present in carriers in the community, and no doubt brought in from outside sources, there is no reason to exclude rheumatic children from sanatoriums because they happen to carry these bacteria. There is no method known to rid carriers of hemolytic streptococci.

The authors propose a new viewpoint of the etiologic relation of hemolytic streptococci to rheumatic fever: It seems possible, they say, that the streptococcic infection may be merely an indication which accompanies the invasion or the reactivation of a hypothetical rheumatic agent. In other words, the entrance or the reactivation of this unknown agent may enhance the infectivity of streptococci, just as the multiplication of the herpes simplex virus is brought about by certain diseases which seem to lower the resistance of a patient.

107. Cannon, P. R.: The Problem of Lipid Pneumonia, J. A. M. A. **115**:2176-2180 (Dec. 21) 1940.

108. Blackford, S. D., and Casey, C. J.: Pleuropulmonary Tularemia, Arch. Int. Med. **67**:43-71 (Jan.) 1941.

109. Moolten, S. E.: Pulmonary Infection and Necrosis in Diabetes Mellitus: Report of a Case of Dissecting Necrotic Pneumonia Complicating Pancreatic Lithiasis, Arch. Int. Med. **66**:561-578 (Sept.) 1940.

110. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three Year Study, J. Clin. Investigation **20**:273-287 (May) 1941.

Thomson and Innes ¹¹¹ found hemolytic streptococci in injured heart valves in 5 of 10 rheumatic patients studied at necropsy. The frequent presence of the organisms, they believe, indicates their probable etiologic connection with rheumatic fever, for they were not found in undamaged valves. On the other hand, the associated lesions are unlike those characteristic of the usual streptococcic infection.

A filtrate of hemolytic streptococci used as a vaccine was said to have had continued beneficial effect on the course of rheumatic fever after six years.¹¹² The data, however, seem hardly impressive enough to warrant conclusions.

In Brown and Wolff's ¹¹³ series of 175 patients with acute rheumatic fever 50 per cent showed no evidence of permanent damage to the heart after periods of four to eleven years. This favorable proportion is much larger than most authors report, and one wonders if the patients had been observed long enough. Many more years than mentioned may elapse before cardiac disease becomes evident.

BACILLARY DISEASE

Bacillary Dysentery.—The intimate relation of outbreaks of dysentery to famine or other hardship has long been recognized. It was assumed, perhaps correctly, that the resultant lowered resistance of the body permits invasion of the bacilli and disease follows. Recent experiments have apparently uncovered one of the responsible factors.¹¹⁴ Langston and his associates noted the development of diarrhea, anemia and leukopenia in monkeys fed a vitamin-deficient diet. Addition of various known vitamins failed to cure the condition, but some factor present in dried yeast and crude liver extract produced improvement. The unknown curative substance was labeled vitamin M. In subsequent studies by Janota and Dack, monkeys given large doses of dysentery bacilli were not infected unless the diet was deficient in vitamin M. Furthermore, in healthy monkeys which were carriers of dysentery bacilli the disease developed only when the diet was restricted. These results were confirmed by Day and his associates. The application of this knowledge to human dysentery is worthy of immediate study.

Deficiency in diet, on the other hand, need not play an important role in the causation of dysentery. An explosive outbreak of 97 cases of the disease due to the Newcastle bacillus occurred in a hospital in New

111. Thomson, S., and Innes, J.: Hemolytic Streptococci in Cardiac Lesions of Acute Rheumatism, *Brit. M. J.* **2**:733-735 (Nov. 30) 1940.

112. Wasson, V. P., and Brown, E. E.: Immunization Against Rheumatic Fever with Hemolytic Streptococcus Filtrate, *Am. Heart J.* **20**:1-11 (July) 1940.

113. Brown, M. G., and Wolff, L.: Recovery from Acute Rheumatic Fever Without Permanent Cardiac Damage, *New England J. Med.* **223**:242-244 (Aug. 15) 1940.

114. Avitaminotic Dysentery, editorial, *J. A. M. A.* **116**:2169 (May 10) 1941.

York city, chiefly among healthy young adults.¹¹⁵ The infection was apparently spread by food contaminated by an undetected carrier in the kitchen of the nurses' home. The constitutional symptoms in some cases were more severe than in cases of disease caused by the Flexner or the Sonne strain. The outbreak affords further proof of the pathogenicity of the Newcastle variety of dysentery bacilli.

Brucellosis.—Wise and Poston¹¹⁶ report on further studies concerning the presence of *Brucella melitensis* in the lymph nodes of 14 patients with Hodgkin's disease. Although there is no evidence to favor an etiologic relation, as the authors once claimed, they suspect that the bacterial infection influences the course of Hodgkin's disease, but just how is difficult to see.

Negative results attended efforts to determine the antigenicity of brucellas given by mouth.¹¹⁷ Agglutinins developed only after rabbits had been vaccinated parenterally. There is, therefore, no support for the oral use of vaccine.

Mexican investigators¹¹⁸ obtained promising results in the treatment of caprine brucellosis with parenteral injection of antigen prepared by grinding brucella organisms of the three varieties, *B. melitensis*, *B. abortus* and *B. suis*. Treatment was adjusted to avoid reactions. The results, though favorable, were not as impressive as those reported by other observers.

Meyer and Eddie^{118a} gathered reports of 74 cases of brucellosis contracted by laboratory workers. The handling of cultures or specimens and the inhalation of brucellas in dust are dangerous. About one half of the victims were sick for a week, but some were invalids for months. Vaccine failed to immunize exposed persons.

Typhoid Fever.—Lazarus¹¹⁹ confirms the reliability of the method of Craigie and Yen for the typing of typhoid bacilli. By use of this

115. Hardy, A. V.; Frant, S.; Jarcho, S. W., and Schlosser, E. G.: Studies of the Acute Diarrheal Diseases: IV. An Outbreak of Bacillary Dysentery Due to the "Newcastle Dysentery Bacillus," Pub. Health Rep. **55**:2101-2116 (Nov. 15) 1940.

116. Wise, N. B., and Poston, M. A.: The Coexistence of *Brucella* Infection and Hodgkin's Disease: A Clinical, Bacteriologic and Immunologic Study, J. A. M. A. **115**:1976-1984 (Dec. 7) 1940.

117. Hageman, P. O., and Doubly, J. A.: Variations in Immune Response to *Brucella Abortus*, Depending upon the Route of Administration, Proc. Soc. Exper. Biol. & Med. **45**:801-802 (Dec.) 1940.

118. Castaneda, M. R., and Cardenas, C.: Treatment of Brucellosis with *Brucella* Antigens, Am. J. Trop. Med. **21**:185-190 (March) 1941.

118a. Meyer, K. F., and Eddie, B.: Laboratory Infections Due to *Brucella*, J. Infect. Dis. **68**:24-32 (Jan.-Feb.) 1941.

119. Lazarus, A. S.: Typing of Typhoid Bacilli in Nine Western States by Bacteriophage Method of Craigie and Yen, Proc. Soc. Exper. Biol. & Med. **45**:400-402 (Oct.) 1940.

method, which is based on certain peculiarities of a strain of bacteriophage specific for the Vi form of *Bacillus typhosus*, it is possible to classify strains into readily distinguishable types, designated in alphabetic order from A to J and by a few other letters. In the paper discussed, 97 per cent of strains fell into types A, B, C, D, E and F. In studies thus far made, the various types have been stable. It is, of course, of as much importance epidemiologically to type typhoid bacilli as it is to type pneumococci, hemolytic streptococci and other bacteria which have thus been classified. It is, however, difficult to reconcile the authors' views as to a "strain of bacteriophage" with the conclusions of Krueger and Scribner that bacteriophage appears to be formed from a precursor originating within the bacterium, as discussed in the section entitled "Miscellaneous Studies."

Results of studies at the Army Medical School, Washington, D. C.,¹²⁰ show that it is necessary to revaccinate at yearly intervals to maintain a high immunity to typhoid. The interval should not exceed two years, and vaccination should not be withheld because of age or many previous vaccinations.

Several instances are reported of apparent cure of the carrier state by treatment with soluble iodophthalein¹²¹ and with sulfaguanidine.¹¹ In the face of many previous unsuccessful methods employed, including surgical removal of the gallbladder, these comparatively harmless ones deserve further trial.

Recent comment¹²² emphasizes the striking decline in the national death rate from typhoid fever, from 34 deaths per 100,000 in 1900 to 2 per 100,000 at present. In some southern states the disease is still not fully under control, because of the difficulties in disposal of human waste in rural districts.

Tetanus.—Vener and Bower¹²³ report a surprisingly low mortality rate (29 per cent) among 100 cases of tetanus. It may be pointed out, however, that the great majority of their patients were less than 14 years old, and hence of the age for which the mortality is naturally low. The authors prescribe a rather standardized regimen and seemingly ignore the important contributions and views of Abell. They recommend a

120. Longfellow, D., and Luippold, G. F.: Typhoid Vaccine Studies: Revaccination and Duration of Immunity, *Am. J. Pub. Health* **30**:1311-1317 (Nov.) 1940.

121. Saphir, W., and Howell, K. M.: Soluble Iodophthalein in Treatment of Carriers of Typhoid-Paratyphoid Group, *J. A. M. A.* **114**:1988-1990 (May 18) 1940. Enright, J. R.: Apparent Cure of Typhoid Carriers with Soluble Iodophthalein, *ibid.* **115**:220 (Jan. 18) 1941.

122. The Eradication of Typhoid Fever, *Statist. Bull. Metrop. Life Ins. Co.* **21**: 6-8 (Aug.) 1940.

123. Vener, H. I., and Bower, A. G.: Clinical Tetanus: Treatment in One Hundred Consecutive Cases with a Net Mortality Rate of Nineteen Per Cent, *J. A. M. A.* **116**:1627-1631 (April 12) 1941.

total dose up to 200,000 American units of tetanus antitoxin, some of it administered intracisternally, and also local injection at the site of entry to serve as "a possible barrier to the progress of toxin along the course of the nerve trunks," an unlikely mode of transport. However, the most questionable of the procedures recommended is the use of methenamine, for highly hypothetical reasons cloaked in words which mystify rather than clarify.

After Abel's experiments, which seemed so convincing and reasonable, in attempting to contradict the Meyer-Ransom theory of the transmission of tetanus toxin by way of nerves, a new group of investigators^{123a} now presents results which reverse the hypothesis. According to Friedemann, Hollander and Tarlov, tetanus toxin does not reach the central nervous system by way of the blood, as Abel claimed to have proved; tetanus cannot be explained by the action of toxin on the sensory nerve endings, and tetanus toxin can travel through nerves. In spite of the evidence presented, Abel's views, to me at least, seem more logical. It is hoped that the matter will eventually be settled.

Plague.—It is well known that plague is enzootic in many species of rodents in western United States. Two small epizootic outbreaks of plague,¹²⁴ one in Utah and one in New Mexico, occurred among squirrels. The only instance of the disease reported in human beings occurred in a boy in Idaho.¹²⁵ Murdock¹²⁶ described three outbreaks in Ecuador in 1939, in which there were 38 deaths. Pneumonic plague occurred in only one epidemic. Physicians in any area where pneumonic plague is endemic are warned to suspect the disease in any patient who is alleged to have pneumonia, but who dies within four days or has a slight soft easy cough, with flecks of pus in the sputum. Bloody sputum occurs in the late stages of the disease. Pneumonic plague almost always originates from patients with the bubonic form in whom secondary pneumonia develops. Both forms of the disease occurred in northern Argentine provinces last year.¹²⁷

Infection Caused by Bacillus Violaceus.—Schattenberg and Van Brown¹²⁸ refer to 2 cases of infection in human beings caused by *B.*

123a. Friedemann, U.; Hollander, A., and Tarlov, I. M.: Investigation on the Pathogenesis of Tetanus III, *J. Immunol.* **40**:325-364 (March) 1941.

124. Byington, L. B.: Two Epizootics of Plague Infection in Wild Rodents in the Western United States in 1938, *Pub. Health Rep.* **55**:1496-1501 (Aug. 16) 1940.

125. Bubonic Plague, *Medical News* (Idaho), *J. A. M. A.* **115**:867 (Sept. 7) 1940.

126. Murdock, J. R.: Pneumonic Plague in Ecuador During 1939, *Pub. Health Rep.* **55**:2172-2178 (Nov. 22) 1940.

127. Bubonic Plague, *Foreign Letters* (Buenos Aires), *J. A. M. A.* **115**:871 (Sept. 7) 1940.

128. Schattenberg, H. J., and Van Brown, D.: Experimentally Produced Wounds as a Route of Fatal Infection Caused by *Bacillus Violaceus*, *Proc. Soc. Exper. Biol. & Med.* **46**:478-482 (March) 1941.

violaceous and report a case of their own. This bacterium, usually regarded as a nonpathogenic saprophyte, may at times cause disease. In experimental studies, the infection was transmitted to mice, guinea pigs and rabbits by application of living organisms to abraded skin.

ARTHRITIS

In my review of 1935,¹²⁹ I mentioned the enigma of the reported presence of streptococci in the blood of patients with rheumatoid arthritis or rheumatic fever. Some authors observed the organisms in 50 per cent of cases, but others seldom encountered bacteremia. The problem now seems to be less obscure. In carefully controlled studies, Cecil and his co-workers¹³⁰ were unable to isolate any significant bacteria from the blood of patients with either disease. Cecil¹³¹ therefore retracts his previous statements and now suggests that perhaps the streptococci which he formerly thought to be present in these diseases represented contaminants from unsterile pipets. It would be of interest to hear from other investigators, notably Clawson and Wetherby, whose work several years ago seemed to confirm that of Cecil. Wetherby,¹³² as a matter of fact, still clings to the view that streptococcus vaccine is of value in the treatment of rheumatoid arthritis. He reports improvement in the now familiar 75 per cent of patients as a result of such treatment. This percentage of improvement is about what one expects after any form of treatment, or after no treatment at all, for it reflects the natural course of the disease. In the panel discussion on arthritis at the recent meeting of the American College of Physicians in Boston, Bauer, Colebrook and Hench minimized the value of vaccine, and one of them did not advocate the use of vaccine at all.

Smyth and his collaborators¹³³ tested the effect on patients with arthritis of roentgen therapy under controlled conditions and report discouraging results. Most of the physicians who discussed the paper were in agreement but expressed the opinion that in some cases roentgen therapy relieved pain.

Anderson and Palmer¹³⁴ sound another warning against the use of gold compounds in treatment and report a case in which the outcome

129. Reimann, H. A.: Infectious Diseases, *Arch. Int. Med.* **56**:382-411 (Aug.) 1935.

130. Angevine, D. M.; Rothbard, S., and Cecil, R. L.: Cultural Studies on Rheumatoid Arthritis and Rheumatic Fever, *J. A. M. A.* **115**:2112-2113 (Dec. 14) 1940.

131. Cecil, R. L., in discussion on Angevine, Rothbard and Cecil.¹³⁰

132. Wetherby, M.: Intravenous Streptococcic Vaccine Treatment of Chronic Rheumatoid Disease, *Ann. Int. Med.* **14**:1849-1857 (April) 1941.

133. Smyth, C. J.; Freyberg, R. H., and Peck, W. S.: Roentgen Therapy for Rheumatic Disease, *J. A. M. A.* **116**:1995-2001 (May 3) 1941.

134. Anderson, N. L., and Palmer, W. L.: The Danger of Gold Salt Therapy: Report of a Fatal Case, *J. A. M. A.* **115**:1627-1630 (Nov. 9) 1940.

was fatal. Sabin,¹³⁵ however, prepared a nontoxic compound, calcium aurothiomalate, which gave striking results in curing mice with arthritis caused by a pleuropneumonia-like micro-organism. Arthritis disappeared completely in 90 per cent of 70 mice treated with large doses (1 mg.) of the salt; there was no improvement in 30 control mice. It is not possible to state without trial whether beneficial effects might also occur in human subjects with arthritis similarly treated and whether the substance is nontoxic for human beings, as well as for mice. According to Dawson,¹³⁶ arthritis in rats caused by pleuropneumonia-like organisms is quite different from arthritis in human beings.

At a meeting of the Association of American Physicians in May, gold salts were said by Cecil, Dawson and Wainwright to be the most effective of any remedy thus far used. Bauer was less enthusiastic. Toxic effects, particularly dermatitis, were reported as common.

Hench¹³⁷ reported a series of 34 cases of recurring arthritis in which the joints were apparently not permanently injured, even after many attacks. The disease was characterized by repeated attacks of short duration, with little or no constitutional reaction or abnormality as reflected in the results of laboratory tests. Whether the disease is an entity separate from other forms of arthritis was undecided. The disease was not influenced by any of the following forms of treatment: administration of ephedrine, epinephrine, amphetamine or ergotamine tartrate; removal of supposed foci of infection; injection of autogenous vaccine; low protein diet; administration of histaminase; injection of typhoid vaccine, and others.

NEUROTROPIC VIRUSES

Toomey¹³⁸ tabulates numerous differential features by which the various forms of encephalitis may be recognized. The data given are particularly valuable in the recognition of such newly discovered entities as lymphocytic choriomeningitis, St. Louis encephalitis, Japanese type B encephalitis, Australian X disease and equine encephalitis. Webster gives an etiologic classification.^{138a} Two new viruses which attack the nervous system have been reported. One, discovered by Russians,¹³⁹ was

135. Sabin, A. B.: The Therapeutic Effectiveness of a Practically Nontoxic New Compound (Calcium Aurothiomalate) in Experimental Proliferative Chronic Arthritis of Mice, *Science* **92**:535-536 (Dec. 6) 1940.

136. Dawson, M. L., in discussion on Angevine, Rothbard and Cecil.¹³⁰

137. Hench, P. S.: An Oft Recurring Disease of Joints (Arthritis, Periarthritis, Para-Arthritis) Apparently Producing No Articular Residues, to be published.

138. Toomey, J. A.: Differential Diagnosis of Various Forms of Encephalitis, *J. A. M. A.* **115**:1985-1989 (Dec. 7) 1940.

138a. Webster, L. T.: Classification of Primary Encephalitides of Man According to Virus Etiology: Present Status, *J. A. M. A.* **116**:2840-2841 (June 28) 1941.

139. Chumakov, M. P., and Seitlenok, N. A.: Tick-Borne Human Encephalitis in the European Part of U. S. S. R. and Siberia, *Science* **92**:263-264 (Sept. 20) 1940.

found to be transmitted by ticks and to be similar to the so-called Far East tick-borne vernoestival encephalitis. The disease affects woodsmen and hunters in the warm months. The second virus was isolated from patients in Uganda.¹⁴⁰ The disease was named Bwamba fever, and its causative filtrable virus was readily transmitted to mice and monkeys. Lesions in mice were limited to the nervous system.

Other Russians, in 1935, isolated a virus which they regarded as belonging to the group of viruses causing American equine encephalitis. According to Howitt,¹⁴¹ this virus should actually be classified with rabies viruses, because of its serologic and immunologic reactions, the size of its particles, its absence from the blood and organs, its ability to infect dogs and its cytoplasmic inclusions.

Lymphocytic Choriomeningitis.—Howard¹⁴² shows that this disease, like other infections, has various gradations of severity. She cites the work of Lepine, who inoculated patients with dementia paralytica with the virus. Fever and influenza-like symptoms appeared after thirty-six to seventy-two hours, but signs of meningeal involvement developed in only half of the patients, and then only after fifteen days or more. The disease in general can be classified as (a) a mild form without meningeal signs, (b) acute benign lymphocytic meningitis and (c) meningo-encephalitis, which is sometimes rapidly fatal. Armstrong and Hornbrook⁸⁴ report a case of lymphocytic choriomeningitis without meningeal symptoms (see page 342). Other authors¹⁴³ describe a case of the disease lasting four months, during which time there were four recurrences. Because in each of the five attacks a fall in temperature and improvement followed the administration of sulfanilamide, it was suggested that the drug might have had a specific effect. On the other hand, the disease may disappear spontaneously after several days.

Poliomyelitis.—Attempts to devise a simpler method than the virus neutralization test for the identification of the virus of poliomyelitis were unsuccessful.¹⁴⁴ For a time it seemed as if Armstrong's success in transmitting the Lansing strain to rodents would solve the problem.

140. Smithburn, K. C.; Mahaffy, A. F., and Paul, J. H.: Bwamba Fever and Its Causative Virus, *Am. J. Trop. Med.* **21**:75-90 (Jan.) 1941.

141. Howitt, B.: Relationship of Moscow Q Virus of Equine Encephalomyelitis to Rabies, *Proc. Soc. Exper. Biol. & Med.* **46**:69-73 (Jan.) 1941.

142. Howard, M. E.: Infection with the Virus of Choriomeningitis in Man, *Yale J. Biol. & Med.* **13**:161-180 (Dec.) 1940.

143. Leichenger, H.; Milzer, A., and Lack, H.: Recurrent Lymphocytic Choriomeningitis Treated with Sulfanilamide, *J. A. M. A.* **115**:436-440 (Aug. 10) 1940.

144. Raffel, S., and Schultz, E. W.: Immunological Reactions in Poliomyelitis, *J. Immunol.* **39**:265-275 (Oct.) 1940.

Kessel and Stimpert¹⁴⁵ were unable to transmit any other strain to rodents and imply that the results of Jungeblut and Sanders¹⁴⁶ may be the effect of an incidental virus native in rodents. The last-named investigators,¹⁴⁷ however, report confirmatory evidence that the virus they studied was actually the one of poliomyelitis, but that after passage through cotton rats it had wholly lost its virulence for monkeys. The most important results of these investigations show that monkeys may be partially immunized against the monkey-virulent strain by vaccination with the same strain attenuated by passage through mice. Other confirmatory evidence is at hand in the work of Toomey and Takacs,¹⁴⁸ who succeeded in establishing both Flexner's M.V. strain and his Philadelphia strain in cotton rats. The "acclimated" rat cord virus could be transferred to monkeys. Howitt and van Herick,¹⁴⁹ on the other hand, were unable to transmit either old or newly isolated strains of poliomyelitis virus to cotton rats or to certain varieties of mice.

The observations of Burnet¹⁵⁰ follow along similar lines of "attenuation" or variation. According to him, the virus of poliomyelitis as it affects the human population in Australia has undergone a change. Up to 1920 the disease affected chiefly young children, was of low virulence and high infectivity, and rarely caused paralysis, whereas its age incidence now resembles that of other common infectious diseases of childhood and the virus in general is more neurotropic and less infective and antigenic. However, the question remains whether this interpretation is correct. Did the virus actually change, or, as in acute virus infections of the respiratory tract, do different strains of poliomyelitis virus, prevalent in different years, cause the variations in human sickness?

Jungeblut and Sanders¹⁵¹ report studies on a strain (SK) of the virus of poliomyelitis. After repeated passage in mice, the strain,

145. Kessel, J. F., and Stimpert, F. D.: Attempts to Transmit Poliomyelitis Virus to Rodents, *Proc. Soc. Exper. Biol. & Med.* **45**:665-666 (Nov.) 1940.

146. Jungeblut, C. W., and Sanders, M.: Isolation of a Murine Neurotropic Virus by Passage of Monkey Poliomyelitis Virus to Cotton Rats and White Mice, *Proc. Soc. Exper. Biol. & Med.* **44**:375-378 (June) 1940.

147. Jungeblut, C. W., and Sanders, M.: Studies of a Murine Strain of Poliomyelitis Virus in Cotton Rats and White Mice, *J. Exper. Med.* **72**:407-436 (Oct.) 1940.

148. Toomey, J. A., and Takacs, W. S.: Poliomyelitis Virus Acclimated to Small Laboratory Animals, *Proc. Soc. Exper. Biol. & Med.* **46**:22-25 (Jan.) 1941.

149. Howitt, B. F., and van Herick, W.: Attempted Adaptations of the Virus of Poliomyelitis to Wild Rodents, *Proc. Soc. Exper. Biol. & Med.* **46**:431-435 (March) 1941.

150. New Light on Poliomyelitis, *Foreign Letters (Australia)*, *J. A. M. A.* **116**:244 (Jan. 18) 1941.

151. Jungeblut, C. W., and Sanders, M.: Transmission of a Murine Strain of Poliomyelitis Virus to Guinea Pigs and Rhesus Monkeys, *J. A. M. A.* **116**:2136-2139 (May 10) 1941.

previously not pathogenic for guinea pigs and monkeys, became so. In undergoing the change the nature of the virus varied in certain respects, depending on its residence in different hosts, but serologically it remained the same. Although pathogenicity of the virus for guinea pigs was established, continued passage in these animals caused it to deteriorate and disappear. While the virus was active in guinea pigs, it could be returned easily to mice and to cotton rats, but not to monkeys. As it deteriorated in the guinea pig, pathogenicity for monkeys reappeared, a change which suggested that a cyclic variation had occurred. The virus also seems to evoke a latent immunity in guinea pigs which protects them against subsequent infection with a virulent strain. The evidence of the complex biologic properties and variability of the virus gained in these experiments may help to clarify some of the mysterious problems regarding infection and epidemiology in man.

Howe and Bodian¹⁵² propose a simplified technic for isolating the virus of poliomyelitis from stools. Untreated stools are emulsified in water and frozen with solid carbon dioxide. One cubic centimeter of the thawed emulsion is then dropped into the nares of monkeys and gently rubbed in. By this technic virus was recovered from ten or fourteen samples of stool during an epidemic in Baltimore. The average period of incubation was two weeks.

Lumsden¹⁵³ shows how untrustworthy the reported diagnoses of cases of poliomyelitis may be, a situation already discussed with reference to pneumonia.⁹² In a study of 34 cases reported in Tennessee, he found that the diagnosis was wrong in 6, was doubtful in 11 and, justified by clinical data and results of such laboratory studies as were made, could be accepted as correct in only 17.

He made little progress in the course of his search for the source of infection. No 2 cases of the disease in human beings occurred in the same household, and in no case was there suggestion of direct conveyance from the sick to the well. In 3 instances, however, the disease in human beings was coincident with a paralytic condition of the legs or wings of several chickens on the premises. The diseases may or may not have been unrelated.

The effect of trauma and strain as contributing causative factors in poliomyelitis is summarized in an editorial.^{153a}

152. Howe, H. A., and Bodian, D.: Portals of Entry of Poliomyelitis Virus in the Chimpanzee, *J. Infect. Dis.* **66**:198-206 (May-June) 1940.

153. Lumsden, L. L.: "Sporadic" Poliomyelitis, *Pub. Health Rep.* **56**:992-1007 (May 9) 1941.

153a. Trauma and Strain in Relation to Poliomyelitis, editorial, *J. A. M. A.* **116**:2506-2507 (May 31) 1941.

A case of an infant with acute encephalitis was described; the virus of herpes simplex was isolated in mice from brain tissue taken at necropsy, and typical intranuclear inclusions were found in the brain cells.¹⁵⁴

Equine Encephalitis.—A second case of western equine encephalitis resulted from an infection contracted by a laboratory worker when living chick embryo virus was accidentally sprayed over him.¹⁵⁵ The incubation period was fourteen days. Death occurred on the eighth day. Although it is generally held that specific therapy is of no therapeutic value in diseases caused by viruses, a specific hyperimmune rabbit serum apparently cured a large percentage of mice infected with western encephalitis virus, as compared with a mortality rate of 100 per cent among untreated animals.¹⁵⁶ According to Davis,¹⁵⁷ several species of mosquitoes, and most of the genus *Aedes*, can carry the virus. The eastern form of the disease could be transmitted to sparrows and pigeons. These observations suggest that insects may be responsible for the conveyance of the infection among birds, animals and human beings. The virus of the eastern form appears to be composed of a complex which is of high molecular weight and consists of phospholipids, cholesterol, fatty acid and ribonucleoprotein.¹⁵⁸ A vaccine which protects animals against experimental infection has been purified and concentrated.¹⁵⁹

Horses may also be a source of infection for St. Louis encephalitis in man. The blood of normal horses occasionally contains antibodies specific for the virus, and horses are susceptible to experimental infection.^{159a}

154. Smith, M. G.; Lennette, E. H., and Reames, H. R.: Isolation of the Virus of Herpes Simplex and the Demonstration of Intranuclear Inclusion in a Case of Acute Encephalitis, *Am. J. Path.* **17**:55-67 (Jan.) 1941.

155. Helwig, F. C.: Western Equine Encephalomyelitis Following Accidental Inoculation with Chick Embryo Virus: Report of Fatal Human Case with Necropsy, *J. A. M. A.* **115**:291-292 (July 27) 1940.

156. Zichis, J., and Shaughnessy, H. J.: Experimental Western Equine Encephalomyelitis: Successful Treatment with Hyperimmune Rabbit Serum, *J. A. M. A.* **115**:1071-1078 (Sept. 28) 1940.

157. Davis, W. A.: Study of Birds and Mosquitoes as Hosts for the Virus of Eastern Equine Encephalomyelitis, *Am. J. Hyg. (Sect. C)* **32**:45-59 (Sept.) 1940.

158. Sharp, D. G.; Taylor, A. R.; Beard, D.; Finkelstein, H., and Beard, J. W.: Properties of Isolated Equine Encephalomyelitis Sera (Eastern Strain), *Science* **92**:359-361 (Oct. 18) 1940.

159. Taylor, A. R.; Sharp, D. G.; Beard, D.; Finkelstein, H., and Beard, J. W.: Concentration and Partial Purification of Equine Encephalomyelitis Vaccines, *Science* **92**:586-587 (Dec. 20) 1940.

159a. Cox, H. R.: Susceptibility of Horses to St. Louis Encephalitis Virus, *Pub. Health Rep.* **56**:1391-1392 (July 4) 1941.

UNUSUAL INFECTIONS CONTRACTED FROM ANIMALS

Milker's Nodules.—Becker's¹⁶⁰ report of 4 cases of this condition, occurring in Minnesota, is the first record of it in the American literature. He reviewed the extensive European, chiefly German, work on the subject. It is surprising that little or no attention has been given to the matter in this country, since it is an occupational disease of milkers, and may be widely distributed among dairymen. The nodules may vary from one to forty on hands which come in contact with infected udders. There is little or no systemic reaction. The disease is probably caused by a virus and is thought by some to be related to vaccinia or to variola, but no evidence supports this view. One attack confers immunity.

Ecthyma Contagiosum.—Only 1 case of this condition was recorded in the American literature before the 2 cases reported by Nomland¹⁶¹ from Iowa. The disease is caused by a filtrable virus, has worldwide prevalence among sheep and is characterized by ulcerative lesions around the mouth, nostrils and udder. Secondary infection may be serious. It is probable that this disease, like milker's nodules, may be widespread among sheep ranchers, but is so mild that it attracts little attention. In both cases reported by Nomland pustules and ulcers developed on the hands. There were no constitutional symptoms.

Boisvert and Fousek¹⁶² report a case of infection caused by *Pasteurella lepisepctica* and contracted from the bite of a rabbit in a research laboratory. It is difficult to understand why the wound was cauterized with nitric acid a day later. Even if it was done to prevent rabies, the gesture seems futile, if not actually harmful.

Leptospirosis.—The first report of leptospirosis contracted in polluted water in this country was made by Havens and associates.¹⁶³ Seven young men contracted the disease while bathing in contaminated water; the attack was mild in 5 of them, severe in 1 and fatal in 1. Another report,¹⁶⁴ of a large group of cases of jaundice in Pennsylvania, is confused and uncertain. Apparently cases of the condition known as acute catarrhal jaundice are included in the group.

160. Becker, F. T.: *Milker's Nodules*, J. A. M. A. **115**:2140-2143 (Dec. 21) 1940.

161. Nomland, R.: *Human Infection with Ecthyma Contagiosum, a Virus Disorder of Sheep: Report of Two Cases*, Arch. Dermat. & Syph. **42**:878-883 (Nov.) 1940.

162. Boisvert, P. L., and Fousek, M. D.: *Human Infections with Pasteurella Lepisepctica Following a Rabbit Bite*, J. A. M. A. **116**:1902-1903 (April 26) 1941.

163. Havens, W. P.; Bucher, C. J., and Reimann, H. A.: *Leptospirosis: A Public Health Hazard; Report of a Small Outbreak of Weil's Disease in Bathers*, J. A. M. A. **116**:289-291 (Jan. 25) 1941.

164. Learn, B. G.: *A Clinical Report of an Epidemic of Acute Infectious Jaundice*, Pennsylvania M. J. **44**:18-20 (Oct.) 1940.

The albino deer mouse (*Peromyscus maniculatus*) was found to be the most suitable animal among thirty-two species tested for the laboratory diagnosis of leptospirosis.¹⁶⁵ The infection became evident within one to five days. The common white rat is resistant.

Schistosomiasis.—This is another infection which may possibly be contracted by bathing in infected water. *Schistosomum Douthitti* causes "swimmers' itch" when the cercariae penetrate the skin. Brackett believes that penetration may go no farther than the skin, because none of the organisms was found in an artificially infected monkey. Experiments by Penner,¹⁶⁶ however, indicate that systemic infection may occur. Migrating worms were found abundantly in the lungs of a monkey after it had been immersed in water infected with the twenty-four hour cercarial output of twenty-eight snails. The snails came from a pond in Minnesota.

Leishmaniasis.—Chung¹⁶⁷ reports the results of further important studies on the relation of human and canine kala-azar in Peiping. He believes the leishmanias causing the two diseases are identical. Apparently dogs are the reservoir of infection, which may be conveyed to man by the bite of the sand fly.

Dogs, incidentally, appear to be an important source for several diseases of human beings other than rabies and infection caused by the paratyphoid bacillus, namely, leptospirosis, leishmaniasis and coccidioidomycosis. Farness⁶⁵ encountered spontaneous coccidioidomycosis in 2 dogs in Arizona and suggests the possible transmission of infection by household pets.

Rabies.—An incubation period of one hundred and thirteen days was reported¹⁶⁸ in the case of a dog bitten by another rabid dog. In this disease, as in tetanus and in certain other infections, one wonders if the long period of latency is actually the incubation period. It seems possible that the infecting agent may lie dormant for even longer periods and become invasive when something occurs to reduce the resistance of the host or to permit the multiplication and enhancement of the virus, as is thought to happen in herpes simplex. The incubation properly begins when invasion occurs, but in most cases there is no way to

165. Packchianian, A.: Susceptibility and Resistance of Certain Species of American Deer Mice, Genus *Peromyscus*, and Other Rodents to *Leptospira Ictero-haemorrhagiae*, Pub. Health Rep. 55:1389-1402 (Aug. 2) 1940.

166. Penner, L. R.: The Possibilities of Systemic Infection with Dermatitis-Producing Schistosomes, Science 93:327-328 (April 4) 1941.

167. Chung, H. L.: On the Relationship Between Canine and Human Kala-Azar in Peiping, Chinese M. J. 57:501-523 (June) 1940.

168. Long Incubation Period in Rabies, Medical News (California), J. A. M. A. 115:1109 (Sept. 28) 1940.

determine when this happens. Rabies broke out among foxes in Georgia and was contracted by other animals.¹⁶⁹

In experimental studies,¹⁷⁰ Casals observed that the titer of circulating neutralizing antibodies against rabies did not parallel the titer of immunity. Old mice were easier to immunize than young ones.

Psittacosis.—There appear to be, as might be expected, several closely related varieties, or types, of psittacosis virus. Pinkerton and Swank^{81b} discovered a psittacosis-like virus in 5 per cent of 400 pigeons which were given a thiamine-deficient diet. At a meeting of bacteriologists in December 1940, Eaton reported the isolation of a psittacosis-like virus from patients with an atypical form of pneumonia, as mentioned on page 336. It would be interesting to compare these strains with each other and with the so-called "fulmar" psittacosis, isolated from marine birds in the Faroe Islands.¹⁷¹

Because bacteria of the genus *Listerella* (*Bacterium monocytogenes*) produce mononucleosis in the rabbit, a relation between them and the causative organism of human mononucleosis has been suspected. A number of papers have strengthened the theory, but results of recent studies fail to support the view.¹⁷² No significant trend in the agglutinin titer of patient's blood for *Listerella* was demonstrable. Julianelle¹⁷³ discusses the matter in a general appraisal of the subject and states that the relation of the bacterium to mononucleosis must await further study before final decision can be made. Nevertheless, *Listerella* is pathogenic for man and gives rise in most cases to meningoencephalitis.

Toxoplasmosis.—Interest continues in the newly recognized invader of human tissue, the protozoan parasite *Toxoplasma*. It apparently resides naturally in a wide variety of mammals and birds, including rabbits, guinea pigs, mice, rats, squirrels, dogs, monkeys and pigeons. The literature is briefly reviewed by Sabin,¹⁷⁴ who also reports 2 cases of atypical encephalitis in children, 1 in Ohio and the other in West Virginia. The diagnosis was confirmed by recovery of the organism

169. Rabies Among Foxes, Medical News (Georgia), J. A. M. A. **115**:467 (Aug. 10) 1940.

170. Casals, J.: Influence of Age Factors in Immunizability of Mice to Rabies Virus, J. Exper. Med. **72**:453-462 (Oct.) 1940.

171. Rasmussen, R. K.: Ueber eine durch Sturmvögel übertragbare Lungen-erkrankung auf den Färöer, Zentralbl. f. Bakt. (Abt. 1) **143**:93 (Dec. 30) 1938.

172. Janeway, C. A., and Dammin, G. J.: Studies on Infectious Mononucleosis: II. The Relationship of the Organisms of the Genus *Listerella* to the Disease, as Studied by the Agglutinin Reaction, J. Clin. Investigation **20**:233-239 (March) 1941.

173. Julianelle, L. A.: The Function of *Listerella* in Infections, Ann. Int. Med. **14**:608-620 (Oct.) 1940.

174. Sabin, A. B.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**: 801-807 (March 1) 1941.

from mice and guinea pigs after intracerebral and intra-abdominal inoculation of spinal fluid and brain tissue.

Prenatal infection may occur.^{174a}

Pinkerton and Henderson⁸³ report cases of fatal toxoplasmosis in 2 adults in Missouri. Ticks detached shortly before the onset of illness in both cases suggest a possible mode of infection. The disease was characterized by sudden onset, chills, fever, low leukocyte count, a maculopapular eruption and pulmonary involvement. Most of these features are unlike those heretofore described in cases of toxoplasmosis in infants and children, in which encephalitis is prominent. The authors were struck by the resemblance of the disease to typhus and to Rocky Mountain spotted fever and suggest that doubtful cases of the latter disease already recorded should be reinvestigated in the light of this newly discovered entity. They also point out certain similarities between toxoplasmosis in adults and the atypical form of pneumonia described by me and others since 1938. I believe, however, that the similarity extends only as far as interstitial pneumonitis, pulmonary signs and symptoms of atypical pneumonia or pneumonitis are concerned. The bronchioles, alveoli and myocardial fibers in certain sections of cardiac tissue were distended with toxoplasmas. It is probable that diagnosis in certain future cases may be made by demonstrating the organisms in the sputum.

The disease was easily transmitted to guinea pigs by the inoculation of blood obtained from a patient during life and to mice by inoculation with material obtained from the same patient at necropsy. Care must be observed in interpreting results, however, since these animals may harbor toxoplasmas naturally.

Chagas' Disease.—Attention is again directed to the likelihood of unrecognized cases of Chagas' disease occurring in southwestern United States.¹⁷⁵ In 1933 Knifoid and Donat found naturally infected insects in California, and now Packcharian¹⁷⁶ finds them in Texas. The causative organism is a trypanosome which in tissue cells looks like other flagellate protozoa (*Leishmania*, for example) and also like the fungus *Histoplasma*. It is impossible to make a diagnosis on morphologic appearance alone, without cultural studies. Clinically Chagas' disease is characterized in the acute stage by fever, by myxedema and by swelling of the lymph nodes, spleen, liver and thyroid, and in

174a. Wolf, A.; Cowan, D., and Paige, B. H.: Fetal Encephalomyelitis: Prenatal Inception of Infantile Toxoplasmosis. *Science* 93:548-549 (June 6) 1941.

175. Possibility of the Occurrence of Chagas' Disease in the United States, *Comment. Am. J. Trop. Med.* 20:617-618 (July) 1940.

176. Packcharian, A.: Natural Infection of *Triatoma Heidemannii* with *Trypanosoma Cruzi* in Texas. *Pub. Health Rep.* 55:1830-1836 (July 19) 1940.

the chronic stage by myxedema and by symptoms referable to the heart, the endocrine glands and the nervous system.

Rickettsial Diseases.—Because typhus fever is reported with increasing frequency, authors still assume the disease is spreading.¹⁷⁷ It is much more likely that the interest in the disease which comes with increasing knowledge and improvement of methods for diagnosis is chiefly, if not wholly, responsible for the numbers of cases now reported. About 50 per cent of the cases in the United States occur in Georgia. The disease, which centers in small towns and villages, occurs most frequently in the late summer months. The mortality rate is 5 per cent. Rat proofing is the best means of control.

Further studies in the preparation of specific antiserum both against typhus and against Rocky Mountain spotted fever are in progress.¹⁷⁸

After Lewthwaite and Savoor's work in clearing up the confusion about scrub typhus and tsutsugamushi disease, several workers¹⁷⁹ did the same with rickettsial diseases in South Africa. They were able to separate a strain of the murine typhus bacillus from similar ones which were identified as belonging to the group of rickettsias causing Rocky Mountain spotted fever, or *boutonneuse* fever. Such work brings about the desired conformity of terms.

Chinese investigators¹⁸⁰ found, as did those in Australia, that mice and mouse fleas may carry typhus fever.

Colorado Tick Fever.—This interesting disease is shown by Topping¹⁸¹ to be limited in the West to the range and activity of the tick *Dermacentor Andersoni*. It is a mild febrile disease following tick bites and is characterized by aching, photophobia, a period of remission and leukopenia. It resembles dengue, except for the absence of an exanthem and the difference in epidemiologic aspects. The cause of Colorado tick fever has not been found.

177. (a) Bowdoin, C. D., and Boston, R. J.: Preliminary Report on Practical Epidemiology and Control of Endemic Typhus Fever in Georgia, *Am. J. Trop. Med.* **20**:537-550 (July) 1940. (b) Meleney, H.: Recent Extension of Endemic Typhus Fever in Southern United States, *Am. J. Pub. Health* **31**:219-227 (March) 1941.

178. Kurotchkin, T. J.; van der Scheer, J., and Wyckoff, R. W. G.: Refined Hyperimmune Rickettsial Sera, *Proc. Soc. Exper. Biol. & Med.* **45**:323 (Oct.) 1940. Meleney.^{177b}

179. Alexander, R. A.; Mason, J. H., and Neitz, W. D.: Onderstepoort J. Vet. Sc. **119**:13, 1939.

180. Liu, W. T., and Zia, S. H.: Typhus Rickettsia Isolated from Mice and Mouse-Fleas During an Epidemic in Peiping, *Proc. Soc. Exper. Biol. & Med.* **45**:823-826 (Dec.) 1940.

181. Topping, N. H.; Cullyford, J. S., and Davis, G. E.: Colorado Tick Fever, *Pub. Health Rep.* **55**:2224-2237 (Nov. 29) 1940.

MISCELLANEOUS STUDIES

A confusing paper¹⁸² with a confusing title appeared concerning mastoiditis. The author concluded that *Str. hemolyticus* is less virulent in milder climates because evidence gained experimentally indicated that the virulence of solutions of the bacteria kept constantly warm was less than that of solutions subjected to fluctuating temperature, such as is found in northern latitudes. It is evident that the author is unfamiliar with bacteriologic technics and methods of control.

Two authors¹⁸³ discussed the possibility that amebas of varieties usually considered to be nonpathogenic may cause disease. When carbarsone was given, the symptoms supposedly caused by the amebas were said to disappear in a large percentage of patients who harbored them. Most of the critics who discussed the paper were skeptical, and one (Paulson) stated that the studies were not controlled well enough for the results to be significant.

Howell and Knoll¹⁸⁴ found amebiasis to be relatively frequent in Chicago children. In one orphanage nearly 5 per cent of children were carriers. Tobie¹⁸⁵ presents more evidence supporting Craig's view that perhaps all strains of *Endamoeba histolytica*, even though they dwell in "healthy human carriers," are pathogenic. Faust¹⁸⁶ made postmortem examinations of 202 persons who had been killed in accidents to discover by direct observation the incidence of amebiasis in New Orleans. In 13 cases *E. histolytica* was found in actual lesions in the bowel. The lesions themselves were minute, pinpoint ulcers, shallow craters or extensive superficial erosions. It is evident from this study that many persons regarded as symptomless carriers may actually bear extensive, unrecognized ulceration of the bowel.

Lymphogranuloma Venereum.—This disease has been suggested as a possible cause of ulcerative colitis, but Chicago investigators¹⁸⁷ found that only 2 out of 34 patients with venereal lymphogranuloma possessed neutralizing antibodies against the causative virus. It was isolated from

182. Lynch, M. G.: Geographic Virulence of Mastoiditis, *J. A. M. A.* **115**:826-827 (Sept. 7) 1940.

183. Rothman, M. M., and Epstein, H. J.: Clinical Symptoms Associated with the So-Called Nonpathogenic Ameba, *J. A. M. A.* **116**:694-700 (Feb. 22) 1941.

184. Howell, K. M., and Knoll, E. W.: Amebiasis in Infants and Children, *Am. J. Dis. Child.* **61**:54-63 (Jan.) 1941.

185. Tobie, J. E.: Pathogenicity of "Carrier" Strains of *Endamoeba Histolytica* in the Experimental Dog, *Proc. Soc. Exper. Biol. & Med.* **45**:691-693 (Nov.) 1940.

186. Faust, E. C.: Amebiasis in the New Orleans Population as Revealed by Autopsy Examination of Accident Cases, *Am. J. Trop. Med.* **21**:35-48 (Jan.) 1941.

187. Rodaniche, E. C.; Kirsner, J. B., and Palmer, W. L.: *Lymphogranuloma Venereum* in Relation to Chronic Ulcerative Colitis, *J. A. M. A.* **115**:515-519 (Aug. 17) 1940.

2 patients with rectal stricture whose skin reacted to the antigen. A case of chronic conjunctivitis of seven years' duration caused by the virus is reported.¹⁸⁸ Other ocular diseases as well may occur as a result of this infection.¹⁸⁹

South Americans¹⁹⁰ report several cases of possible infection of the digestive tract with the virus of venereal lymphogranuloma. The etiologic relation in most cases was not sufficiently established to be convincing.

Gonococci.—Although the matter of capsulation of gonococci has been a source of controversy for years, Bernstein¹⁹¹ used a special, but simple, method with the usual stains and has shown beyond much doubt that capsules do exist.

Bactericidal Enzymes.—In two papers presented at the May meeting of the American Society for Clinical Investigation, the use of gramicidin as a therapeutic agent was discussed. Gramicidin is an enzyme discovered by Dubos. It is made by a certain soil bacillus and destroys gram-positive bacteria. Unfortunately, it also causes hemolysis, and although heating prevents this undesired change, it also lessens the bactericidal properties. In clinical trial local application of the substance appeared to be of value in controlling superficial infections caused by staphylococci and hemolytic streptococci. Along somewhat similar lines, another substance, called penicillin, derived from a certain strain of the fungus *Penicillium*, was similarly studied. It also had value in controlling superficial infections. Many years ago other investigators studied the effects of extracts of the fungus *Streptothrix* which inhibited the growth of tubercle bacilli, but the work failed to attract attention and was forgotten.

Dubos and Hotchkiss^{191a} show that while gramicidin may cause slow hemolysis of erythrocytes suspended in a solution of sodium chloride, the addition of small amounts of dextrose prevents hemolytic action. They cite other examples of the antagonistic effect of certain microbial cultures

188. Curth, W.; Curth, H. O., and Sanders, M.: Chronic Conjunctivitis Due to the Virus of Venereal Lymphogranuloma, *J. A. M. A.* **115**:445-447 (Aug. 10) 1940.

189. Macnie, J. P.: Ocular Lymphogranuloma Venereum, *Arch. Ophth.* **25**:255-279 (Feb.) 1941.

190. Coutts, W. E.; Opazo, L., and Montenegro, M.: Digestive Tract Infection by the Virus of Lymphogranuloma Inguinale, *Am. J. Digest. Dis.* **7**:287-293 (July) 1940.

191. Bernstein, L. H. T.: Capsulation of *Neisseria Gonorrhoeae*, *Proc. Soc. Exper. Biol. & Med.* **46**:700-703 (April) 1941.

191a. Dubos, R., and Hotchkiss, R. D.: The Production of Bactericidal Substances by Aerobic Sporulating Bacilli, *J. Exper. Med.* **73**:629-640 (May) 1941.

toward unrelated species and report new studies on tyrothricin, a substance obtained from various species of aerobic sporulating bacilli isolated from soil, sewage, manure and cheese. Tyrothricin yields two crystalline substances; one is gramicidin, which is bactericidal for gram-positive bacteria, and the other, tyrocidin, is bactericidal for both gram-positive and gram-negative species. Tyrocidin is perhaps a protoplasmic poison, but gramicidin has a more subtle effect, which is retained against bacteria even in vivo.

Bacteriophage.—Krueger and Scribner¹⁹² continue the important critical analysis of bacteriophage where Eaton and Bayne-Jones left off in 1934. Bacteriophage is apparently a nonvital protein of high molecular weight. It multiplies more rapidly in the presence of living and growing bacteria than do the bacteria themselves, but it may increase even if bacteria do not, so that bacterial growth is not essential for its elaboration. Phage seems to be an enzyme made by cellular synthesis of an inactive precursor, which is later changed to an active form, similar to that of trypsinogen. Bacteriophage is inactivated by colloidal substances of many sorts, including blood, leukocytes, dead bacteria and tissue debris. Krueger suggests that bacteriophage causes dissociation of bacteria, which leads to the development of phage-resistant varieties. I believe that this form of dissociation may be caused by many other substances as well which retard the growth of bacteria or that it may occur spontaneously, as shown in my previous experiments with *Micrococcus tetragenus*. Nevertheless, it is important that phage-resistant forms do appear.

The discussion of the hoped-for practical application of bacteriophage in the treatment of infection is of especial value. The authors' conclusions, with which I concur, are similar to those of Eaton and Bayne-Jones of 1934 and may be summed up in the words of the former:

One is forced to conclude that bacteriophagy in vivo is of rare occurrence . . . therefore with few exceptions . . . it is not logical to rely on the lytic power of the phage in the treatment of disease.

STERILIZATION OF AIR

Robertson and his colleagues¹⁹³ investigated further the important problem of the sterilization of air according to the method of Trillat. Liquid germicidal agents sprayed as fine mist (aerosols) into air con-

192. Krueger, A. P., and Scribner, E. J.: The Bacteriophage: Its Nature and Its Therapeutic Use, *J. A. M. A.* **116**:2160-2167 (May 10); 2269-2277 (May 17) 1940.

193. Robertson, O. H.; Bigg, E.; Miller, B. F., and Baker, Z.: Sterilization of Air by Certain Glycols Employed as Aerosols, *Science* **93**:213-214 (Feb. 28) 1941.

taminated with various bacteria caused a remarkable rapid diminution in the number of floating organisms. English workers used resorcinol and hexylresorcinol. Robertson and associates used propylene glycol and related compounds because of their hygroscopic nature. These were found in themselves to be bactericidal. In carefully controlled tests a concentration of only 1 part of propylene glycol to 2,000,000 volumes of air caused rapid and complete sterilization of air containing 200,000 bacteria per cubic liter. Pneumococci, hemolytic streptococci and other common air-borne bacteria were similarly disposed of.

Studies such as these are of great potential importance, since air-borne infections have been notoriously resistant to epidemiologic control, in contrast with infections transmitted by insects, water and food.

News and Comment

Mississippi Valley Medical Society.—The seventh annual meeting of the Mississippi Valley Medical Society will be held in Cedar Rapids, Iowa, October 1 to 3, 1941, at the Hotel Montrose.

A special feature of the program will be numerous short instructional courses. On October 1 there will be an All-Kansas City program conducted by eight well known clinician-teachers, concluding with a complimentary stag supper; on October 2, the annual banquet, at which Dr. Joseph B. De Lee, emeritus professor of obstetrics and gynecology, University of Chicago, and the presidents of the Illinois, Missouri and Iowa state medical societies will speak, and on October 3, short instructional courses by members of the faculty of the St. Louis University School of Medicine.

Further information may be secured by writing to the secretary-treasurer, Dr. Harold Swanberg, W. C. U. Building, Quincy, Ill.

Dr. Robert B. Lewy, of Chicago, won the first prize (\$100, a gold medal, a certificate award and an invitation to present his essay at the annual meeting of the Mississippi Valley Medical Society) in the fourth annual essay contest of the Mississippi Valley Medical Society "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine." Dr. George A. Skinner, of Berkeley, Calif., was second in the contest, and Dr. Arthur Bowen, of Los Angeles, third; both will receive certificates of merit.

Book Reviews

Enfermedades del riñon (Diseases of the Kidneys). By Jorge Meneses Hoyos, professor at the Mexico School of Medicine and head of the Cardiology Department of the Military General Hospital. Pp. 217. Mexico City: M. L. Sanchez, 1940.

The book, as the author explains in his preface, is intended to present in a short and concise manner the latest developments and accepted progress in the field of renal disease demanding medical treatment. The author has accomplished his task in an excellent way. The first two chapters dealing with the anatomic and physiologic relations of the kidneys are brief, clear and up to date. They are followed by a description of the normal and pathologic relations of the urinary tract and a critical review of the various methods for a functional study of the kidney, with a final paragraph mentioning the author's preferences: for preciseness, Moeller, McIntosh and Van Slyke's method (urea clearance) and Rehberg's test, and for rough estimation McLean's and Fishberg's tests. He speaks appreciatively of Volhard's concentration and dilution test. The chapter on pathogenesis of edema summarizes well the current opinion on the subject. Part 2 commences with a short discussion of the various classifications proposed from time to time for renal diseases. Then follows a brief study of renal disease under the headings of nephritis, nephrosis and nephrosclerosis, with each disease entity as comprised under those terms, clearly outlined. A discussion of conditions of the retina by Dr. A. Zertuche is supplemented by good illustrations. The two excellent final chapters deal with the management of patients by means of diet and diuretics. There is an exhaustive bibliography of American, English, French and German sources, which testifies to the author's wide outlook and painstaking evaluation of controversial material. Good illustrations are interspersed throughout the book.

Clinical Pellagra. By Seale Harris, M.D., Professor Emeritus of Medicine, University of Alabama, Birmingham, Ala.; Assisted by Seale Harris Jr., M.D., formerly Assistant Professor of Medicine, Vanderbilt University, Birmingham, Ala., with foreword by E. V. McCollum, Ph.D., Sc.D., LL.D., Professor of Biochemistry, School of Hygiene and Public Health, the Johns Hopkins University, Baltimore. Price, \$7. Pp. 494, with 70 illustrations. St. Louis: C. V. Mosby Company, 1941.

The following quotation from the foreword, by Dr. E. V. McCollum, clearly states the purpose and scope of this book.

"The book, CLINICAL PELLAGRA, prepared by a close student of pellagrous patients and of the scientific contributions which have thrown light on the nature of the disease, assisted by several distinguished scientists, presents a searching inquiry into the interaction of several agencies secondary to specific dietary deficiencies, which offer a plausible explanation of the complex manifestations with which the clinician meets in pellagrous patients, and particularly in pernicious anemia and sprue."

Section IV, "Clinical Investigations," chapters 15, 16 and 17, written by various members of the staff of the Duke University School of Medicine, adds greatly to the value of this work. There is, however, much repetition throughout the book, perhaps to emphasize the salient features of the disease. The format is attractive, and there are numerous and excellent illustrations and a useful bibliography is appended.

This study is timely because of recent advances in therapy of this disease. It should prove valuable for practitioners of medicine and for students of medicine in the clinical years.

Electrocardiography in Practice. By Ashton Graybiel, M.D., and Paul D. White, M.D. Price, \$6. Pp. 319, with 272 illustrations. Philadelphia: W. B. Saunders Company, 1941.

Despite the recent publication of numerous books on electrocardiography, this excellent work will be welcomed by students and physicians alike. The principles of electrocardiography as they are encountered in everyday practice are presented in a clear and concise manner, and there has been intentional omission of the theoretic detail which so frequently confuses many readers. The electrocardiograms are beautifully reproduced, and the reader has access to two hundred and seventy-two records, representing a wide range of variations. A brief clinical summary of each case and pertinent comments dealing with interpretation are conveniently placed on the page adjoining each graph.

The principles and the technic of electrocardiography are briefly presented, together with a discussion of the electrocardiograms conforming to the criteria established for normality. Part I comprises discussions and examples of innumerable graphic abnormalities and the characteristic electrocardiograms occurring in many diseases and conditions. Adventitious deflections or artefacts, which often confuse and mislead the beginner, are discussed. Part II includes an interesting collection of electrocardiograms, which enables the reader to practice interpretation and then check his conclusions with those of the authors. An appendix, composed of an analytic electrocardiographic index, which details the normal and the abnormal alterations of the various components of the record is included.

The simplicity and comprehensiveness of this book merit its distinction as one of the best yet to appear in its field.

Diseases of the Digestive System. Edited by Sidney A. Portis, M.D., Associate Clinical Professor of Medicine, Rush Medical College, the University of Chicago. Price, \$10. Pp. 952, with 176 illustrations. Philadelphia: Lea & Febiger, 1941.

This book is written by fifty well known authors under the editorship of one. The list of contributors is a veritable "Who's Who" of modern gastroenterology.

The format is agreeable; the illustrations are clear, and the bibliography at the end of each chapter is well selected. The arrangement of the reading matter follows orthodox lines: a preface apologizing for the multiplicity of writers; a brief history of the knowledge of gastrointestinal disease; chapters on the anatomy and physiology of the gastrointestinal tract, and then a succession of articles dealing with almost every phase of how food is or is not digested under abnormal conditions within the abdominal cavity, down to discussions of water brash, whipworm, white bile and Widal hemoclastic shock.

There are two ways of regarding a book of this type. Admittedly, it represents hard work intelligently done. Without doubt, too, students and practitioners will read it, study it and learn much from its contents. Crotchety, old-fashioned physicians may wonder whether knowledge of diseases of the digestive system needs to be expanded to the tune of \$10 into a book nearly a thousand pages long and ask themselves whether a certain amount of padding is not inevitably required to perform such a feat. On the other hand, the editor may be right; perhaps the development of modern scientific gastroenterology has been so rapid that it is difficult for any one person to present the subject in its entirety, in which case a long, many-authored compilation of this type is amply justified.

Frank Howard Lahey: A Birthday Volume. By various authors and sponsors. Pp. 466, with 85 illustrations, figures and tables. Cloth. Privately printed and distributed. Springfield, Ill.: Charles C. Thomas, Publisher, 1940.

This volume, produced by friends of Dr. Lahey and contributed to by numerous friends and pupils, honors Dr. Lahey's sixtieth birthday. It is a well deserved tribute and is beautifully done and uniquely interesting. There is a list of fifty-four authors and thirty-seven sponsors.

The subject matter ranges from a discussion of "Group Medicine and the Lahey Clinic," through numerous medical and surgical essays (there is even a dash of psychiatry) and one or two purely personal messages. Many of the articles deal with thyroid or gastrointestinal surgery, which is proper in view of Dr. Lahey's interest in these fields. There are frequent references to Dr. Lahey's work, which is also proper.

For the most part the essays are rather less formal than the usual medical article. After reading many of them one feels that one has had an informal chat with the author and has received his own impression of the subject, without needlessly cluttering of the issue by references to the literature. One may not always agree with an author, but that does not detract from the value of his discussion.

The publication of this birthday volume in honor of Dr. Lahey was a nice thing to do, and the work has been well done. The authors, the sponsors and Dr. Lahey are all to be congratulated.

The Doctor and the Difficult Child. By William Moodie, M.D., Medical Director London Child Guidance Clinic. Price, \$1.50. Pp. IX + 214. New York: The Commonwealth Fund, 1940.

This is a well written book, divided into four chapters. By way of introduction the author says that it is not a scientific treatise but, rather, an informal discussion of behavior or personality disturbances in children.

At first he defines the importance of a better understanding of juvenile psychology; then he outlines methods of history taking and examination to be used in an approach to mental problems in the young, and finally he describes general principles of psychotherapy employed in pediatrics. The second part of the book is a series of short case reports to illustrate common problems in the behavior of children and how greatly they may be helped by sensible guidance.

The tenor of the book is even and unexaggerated. Due emphasis is laid on the need for recognizing physical illness or serious mental defects as possible bases of behavior difficulties in the young. In the more difficult functional problems, the author's methods of management are sympathetic and rational. It is evident that often the parents need oversight and advice as much as the children.

The book is based on experience acquired in London. But the problems encountered there are evidently no different than the ones met here. People interested in the various phases of child guidance and welfare will enjoy this monograph.

Manual of Physical Diagnosis. By Maurice Lewison, Ellis B. Frelich and George C. Coe. Price, \$3. Pp. 317, with 75 illustrations. Chicago: The Year Book Publishers, Inc., 1940.

This book, small in size, is based on a teaching outline. The book is a praiseworthy attempt to present the essential general diagnostic features of health and disease. General diagnosis is a complicated subject, and an understanding of the signs and symptoms of disease cannot be obtained from such an outline. The book, however, is excellent for purposes of review and should be valuable to students and young physicians and surgeons who are preparing for examinations. As a reference book on general physical diagnosis, it is inadequate.

The Story of Clinical Pulmonary Tuberculosis. By Lawrason Brown, M.D. Price, \$2.75. Pp. 368. Baltimore: The Williams & Wilkins Company, 1941.

Lawrason Brown studied under Osler, in Baltimore, graduating at the turn of the century, and developed his great clinical ability under Trudeau, at Saranac Lake. As a result he combined an abiding fondness for old books and medical history with a thorough training in the art of physical diagnosis at the period of its greatest glory. In his skill in diagnosis he represented perhaps the most perfect flowering of that era. And yet his greatest work was not in the ultra-

refinement of those methods but in the simplification of the diagnosis of tuberculosis for the practitioner and of the treatment for the patient. At the same time that he was collecting old medical books and prints for his library, he was always in the van of the pioneers in new methods, such as the use of roentgen rays in diagnosing and the use of ultraviolet radiation in combating tuberculosis. For lectures and for the book which he might some day find leisure to write he had collected notes before his death, in 1937. Thanks to Mrs. Brown, and to some of his devoted colleagues, this book is now published.

In this day of dependence on roentgenograms of the chest, or even on a mere report of them, for a diagnosis of pulmonary tuberculosis it is both interesting and salutary to read an account of the development of the art of diagnosis in this field. This story is graphically told, with loving attention to the field of physical signs in particular. The chapters on Auenbrugger, Laennec and the stethoscope are especially good. The debt of American medicine in the nineteenth century to the French school is described, with tributes both to the great teachers in Paris and to their students, who became the leading medical men of this country. The discovery and rise of artificial pneumothorax treatment are related with a completeness not available elsewhere.

Homer L. Sampson, who was closely associated with Dr. Brown in the development of the use of the roentgen ray for the diagnosis of pulmonary and intestinal tuberculosis, contributed a chapter on the roentgen rays, in which the development of this essential method of diagnosis from its discovery to the present technic is reviewed in admirably concise form. Edward W. Archibald, of Montreal, wrote the splendid chapter on the development of purely surgical methods of treatment.

One misses the illustrations which might have adorned such a work of medical history. Had Lawrason Brown lived to see this work through the press it would doubtlessly have been illustrated from his library. Moreover, some of the scattered notes comprising the last two chapters would have been worked into the smooth flow of the story in earlier chapters. An excellent index adds greatly to the value of the book for reference. To the shelves of all devotees of medical history and of all those teaching physical diagnosis, to the desk of the medical student and of the tuberculosis specialist, Dr. Brown's last book will be a welcome addition; in fact, it will entertain and instruct in every use of the stethoscope.

Biology of the Laboratory Mouse. By the Staff of the Roscoe B. Jackson Memorial Laboratory, George D. Snell, Editor. Price, \$7. Pp. IX + 497, with 172 illustrations. Philadelphia: P. Blakiston's Sons & Co., 1940.

This reviewer once spent a memorable afternoon with Dr. Maude Slye and was given a personally conducted tour through a town more like one to be found in the kingdom of Lilliput than in the center of a modern city like Chicago. The population of the town was made up entirely of mice. There were slums where the poor and ill-bred lived and, in contrast, fine suburban residences where dwelt in comfort the aristocrats of pedigreed stock, who copulated and otherwise disported themselves according to their own desires. There were hospitals wherein sick mice were painstakingly observed, and where most expert surgical or pathologic procedures were carried out. There was a board of health charged with ferreting out disease and seeing to it that the hygiene of the citizenry was good, that the food supply was proper, that the water supply was pure and that recreational facilities in the form of well ventilated runways were at hand. And, of course, there was an elaborate department of vital statistics. The house in which every citizen resided was tabulated; the number of births, deaths and marriages occurring each day was known, and why or when each one of these major biologic events occurred was noted. In brief, here was a place in which mice could be studied as meticulously as possible.

Since then the laboratory mouse has become a highly respected medical implement. Thus a textbook on his biology and care is by no means unimportant.

The present volume makes interesting reading. It tells all that is known of this small laboratory animal: how he behaves from the time the egg from which he originates is fertilized until his death; his anatomy; the diseases to which he is liable and their pathology; how he reproduces in pure or hybrid strains; how he transmits inheritable characteristics, and even how he should live and be maintained.

The ordinary layman—for the casual physician who enjoys adding to his general store of medical knowledge by diffuse reading is a layman in the field of mouse culture—will appreciate this book. He will realize more clearly than ever how medical knowledge advances and that clinical methods applied to the study of human disease are equally useful when applied to the study of anything else that is alive. To the expert, to any one engaged in the cultivation of the laboratory mouse for use in biologic investigations, this book will make an important manual. It is well written and legibly printed and illustrated. Above all, it is full of sense, knowledge and advice.

Man's Greatest Victory Over Tuberculosis. By J. Arthur Myers, Ph.D., M.D., F.A.C.P., Professor of Medicine and Preventive Medicine and Public Health, University of Minnesota; Chief of Medical Staff, Lymanhurst Health Center, Minneapolis. Price, \$5. Pp. IX + 419, with illustrations, plates and maps. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This book has accurately recorded one of the greatest triumphs of medicine. The author clearly shows how persistent application of sound scientific principles over a prolonged period has resulted in actual control of tuberculosis among cattle and of bovine tuberculosis in human beings. The author cites examples of the many scientific and practical contributions of the veterinary medical profession, with portraits and biographies of leading modern veterinarians and of others associated with the control of disease in domesticated animals. The story of control of bovine tuberculosis is told in clear language and can be enjoyed by the general reading public, although there has been no sacrifice of scientific completeness to adapt the book to this group. The real mission of the book should be one of inspiration to all connected with the current effort to eradicate human tuberculosis by similar methods.

Annual Review of Physiology. By James Murray Luck and Victor E. Hall. Vol. II. Price, \$5. Pp. 784. Stanford University P. O., Calif.: American Physiological Society and Annual Reviews, Inc., 1941.

The third volume of the "Annual Review of Physiology" is planned along the same lines as those of previous years. Some 800 pages are devoted to reviews of twenty-nine major topics in physiology. These reviews are really concentrated abstracts of many articles, and for the most part the reviewers make little attempt at critical evaluation or development of a point of view. For quick orientation, however, this book, as in the past, is invaluable.

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"PRIMARY" HYPOCHROMIC ANEMIA TERMINATING IN PERNICIOUS ANEMIA

REPORT OF TWO CASES

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The possible relation between pernicious anemia and "primary," or "idiopathic," hypochromic anemia has been emphasized in a number of reports. The common denominator in these conditions may lie in a disturbance in the gastric secretion. Castle and his collaborators¹ demonstrated the importance of a defect in gastric secretion in the pathogenesis of pernicious anemia. Davies,² Dameshek,³ Hartfall and Witts⁴ and others found either complete achlorhydria or distinct hypoacidity in the great majority of their cases of "primary," or "idiopathic," hypochromic anemia. It has, furthermore, been noted that complete gastrectomy or a widespread malignant condition of the stomach is not

From the Joseph H. Pratt Diagnostic Hospital and the Blood Clinic, Boston Dispensary.

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1. Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or with Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Role of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, *Am. J. M. Sc.* **182**:741, 1931.

2. Davies, D. T.: Studies on Achlorhydria and Anemia, *Quart. J. Med.* **24**: 447, 1931.

3. Dameshek, W.: (a) Primary Hypochromic Anemia (Erythro-Normoblastic Anemia): A New Type of Idiopathic Anemia, *Am. J. M. Sc.* **182**:520, 1931; (b) Primary Hypochromic Anemia: II. Clinical Features, *J. A. M. A.* **100**:540 (Feb. 25) 1933.

4. Hartfall, S. J., and Witts, L. J.: Gastric Secretion in Simple Achlorhydric and Allied Anemias, *Guy's Hosp. Rep.* **83**:3, 1933.

infrequently followed by the development of either the "liver extract" deficiency or the iron deficiency type of anemia.⁵

The relation between pernicious anemia and "primary" hypochromic anemia was first suspected when it was noted that achlorhydria was often familial.⁶ It was occasionally reported that one or more members of a family had pernicious anemia while others showed hypochromic anemia.⁷ The second, and more direct, line of evidence is presented in the sporadic reports by various observers⁸ of idiopathic hypochromic anemia which has terminated in pernicious anemia. In addition, Buchgraber and Fleischhacker⁹ observed a case of gastric resection in which after fifteen years of hypochromic anemia responding well to iron pernicious anemia developed which was controlled by liver extract therapy. Definite evidence of the transition of one state to another is often difficult to establish, either because the descriptions of the hypochromic anemia are meager or because complications, such as hemorrhage or a malignant condition, may give a hypochromic picture to the otherwise macrocytic character of pernicious anemia.¹⁰

5. (a) Morawitz, P.: Agastrische Anämien und ihre Beziehungen zur Anaemia perniciosa, *Arch. f. Verdauungsk.* **47**:305, 1930. (b) Planteydt, J. M.: Transition of Hypochromic into Hyperchromic Anemia Many Years After Gastric Resection, *Nederl. tijdschr. v. geneesk.* **79**:4153, 1935. (c) Hurst, A. F.: Achlorhydria and Achylia Gastrica, and Their Connection with Addison's Anemia—Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anemia, *Quart. J. Med.* **1**:157, 1932.

6. (a) Oliver, T. H., and Wilkinson, J. F.: Achlorhydria, *Quart. J. Med.* **2**:431, 1933. (b) Wilkinson, J. F., and Brockbank, W.: The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anemia, *ibid.* **24**:219, 1931. (c) Gram, H. C.: Further Observations on a Family Showing Many Cases of Pernicious Anemia, *Acta med. Scandinav.*, 1930, supp. 34, p. 107. (d) Hartfall and Witts.⁴ (e) Hurst.^{5c}

7. (a) Heath, C. W.: The Interrelation of Pernicious Anemia and Idiopathic Hypochromic Anemia, *Am. J. M. Sc.* **185**:365, 1933. (b) Sinkler, W., and Eshner, A. A.: Three Cases of Essential Anemia in One Family—Father and Two Daughters, *ibid.* **112**:287, 1896. (c) Patek, A. J.: Family Pernicious Anemia, *J. A. M. A.* **56**:1315 (May 6) 1911. (d) Bartlett, C. J.: Family Pernicious Anemia, *ibid.* **60**:176 (Jan. 8) 1913. (e) Maclacklan, W. W. G., and Kline, F. M.: The Occurrence of Anemia in Four Generations, *Am. J. M. Sc.* **172**:533, 1926. (f) Hartfall and Witts.⁴ (g) Hurst.^{5c} (h) Wilkinson and Brockbank.^{6b} (i) Gram.^{6c}

8. (a) Schulten, H.: Ueber die essentielle (primäre) hypochrome Anämie. *München. med. Wchnschr.* **85**:1599, 1938. (b) Witts, L. J.: Simple Achlorhydric Anemia, *Guy's Hosp. Rep.* **80**:253, 1930. Dameshek.^{3b} Hartfall and Witts.⁴ Gram.^{6c} Heath.^{7a}

9. Buchgraber, K., and Fleischhacker, H.: Uebergang einer hypochromen Resektionsanämie in Perniziosa, *Wien. Arch. f. inn. Med.* **32**:33, 1938.

10. (a) Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with

The present report deals with 2 cases of "primary," or "idiopathic," hypochromic iron-deficiency anemia which terminated in pernicious anemia. In the first case, in which the Plummer-Vinson syndrome was present and the response to iron was good, typical pernicious anemia responding to liver extract developed several years later. In the second case, which was apparently an instance of typical primary hypochromic anemia, pernicious anemia developed after the administration of iron; in this case, apparently both iron deficiency and liver extract deficiency were simultaneously present, and the administration of iron "unmasked" the underlying macrocytic anemia. The implications of these transitions are discussed.

REPORT OF CASES

CASE 1.—*First Admission.* Lillian D., a 40 year old widow, was admitted to the diagnostic ward of the Boston Dispensary on Jan. 17, 1933, because of weakness and anemia. As a girl, she had been known to have a sallow complexion but was never told she was anemic. She became extremely nervous on the death of her husband, which occurred in 1925, only two years after their marriage. Since 1925, transitory periods of dysphagia occurred, increasing in frequency when she became a secretary for an exacting employer. About five years before her admission to the ward, inability to swallow solid food developed, and her diet became limited to eggs, milk, mush, mashed potatoes and cooked fruit. The patient confessed later that she had an intense dislike for meat even prior to the development of dysphagia because of the thought of the animals being slaughtered. It was also established that one of her nieces, who had a sallow complexion, possessed an aversion to meat and that a first cousin had been treated at another hospital for dysphagia and hypochromic anemia. When the patient was 35, her hair began to turn gray and her finger nails became brittle; the latter symptom was especially troublesome because of her work with the typewriter. Weakness, palpitation, swelling of the ankles and dyspnea on exertion developed. Finally, when pallor became noticeable, about two years before admission, she consulted a physician, who told her she was anemic. Later, diarrhea developed, with five to seven loose stools daily, and a burning sensation of the tongue was felt when fruit juices were taken. During the past four to five years she had noticed that her tongue was often unnaturally red, and during the few months before admission excoriations developed at the angles of the mouth and the tongue became increasingly sore. Until a few years previous to admission her menses had always been regular, but shortly before entry they had become delayed and scant. Paresthesias of the fingers and hands developed in November 1932. About one month previously she had noticed black stools for three days. On admission to the diagnostic ward of the Boston Dispensary on Jan. 17, 1933, and later to the medical ward of the Beth Israel Hospital,¹¹ on January 23, she was found to be pale, with a sallow, parchment-colored skin. There was, however, no icterus. The

Addison's (Pernicious) Anemia, Achlorhydria and Intestinal Infection, *Brain* **45**: 266, 1922. (b) McGregor, H. G.: Pernicious Anemia with Diabetes Mellitus, *Brit. M. J.* **2**:617, 1937. (c) Thyasen, T. E. H.: Ein Fall perniziöser Anämie mit ungewöhnlichen Verlauf, *Klin. Wchnschr.* **7**:1330, 1928.

11. The director of Beth Israel Hospital gave us permission to report the data in this case, which was studied during the senior author's service at that hospital.

hair, which was dyed black, was fundamentally gray. The tongue was completely devoid of coat and papillae and was extremely shiny; it was definitely atrophied and greatly reddened in several areas. At the angles of the mouth, superficial excoriations (*la perlèche*, or cheilosis¹²) were present. The heart was not enlarged; a systolic murmur was present at the apex. The liver and spleen were not felt. The reflexes were normal, and there was no disturbance in the vibration sense. All the finger nails showed vertical ridging; a few were flattened, but there was no definite spooning.

The laboratory data were as follows: The urine gave a negative reaction for albumin and sugar; the fecal urobilinogen content was not increased; four stools gave negative reactions for ova, parasites and occult blood; the Wassermann, Kahn and Hinton reactions of the blood were negative. The blood count showed: hemoglobin concentration, 32 per cent (Sahli); red cells, 4,000,000 per cubic millimeter; white cells, 10,200; platelets, 400,000, and reticulocytes, 2.6 per cent. The red cells showed considerable achromia, with moderate variation in size and shape (fig. 1*A*). They varied in diameter from 4.5 to 10.5 microns, the average cell diameter being 6.90 microns (fig. 2*I*). The red cells were more hypochromic than microcytic. Most of the polymorphonuclear cells had three to six nuclear lobes. The icteric index was 6; the level of serum proteins, 6.08 Gm. per hundred cubic centimeters. The gastric analysis showed an extreme diminution in secretion, with complete achlorhydria after the administration of histamine phosphate.

Time Elapsed After Injection of 1 Cc. of Histamine Phosphate (Minutes)	Volume, Cc.	Free Hydro- chloric Acid	Total Acid	Lactic Acid	Guaiaec
0 (fasting).....	5	0	10	0	0
20.....	10	0	12	..	0
40.....	1	0	14	..	0
60.....	1	0	12	..	0
80.....	5	0	18	..	0

Roentgenograms of the gastrointestinal tract showed slight delay of the barium sulfate meal in the esophagus and a questionable irregularity at the junction of the pharynx with the esophagus. The upper one third of the esophagus showed slight spasm. The remainder of the roentgen examination revealed nothing abnormal.

The diagnosis of primary hypochromic anemia with the Plummer-Vinson syndrome was made.

Clinical Course (fig. 3): During the first ten days of the patient's stay at the Beth Israel Hospital, she was given, in addition to a bland diet, the extract from 1 pound (0.45 Kg.) of meat daily, with little or no response. During the next six day period the patient received 150 Gm. of powdered hemoglobin daily. This medication was discontinued because of severe diarrhea. During the next eight days fresh whole beef blood obtained from the slaughterhouse was given in amounts of 250 cc. four times daily. At the end of this twenty-four day period the blood picture was essentially unchanged, although there had been a slight rise in hemoglobin (hemoglobin concentration 43 per cent, red blood cells 4,200,000). There was no definite reticulocyte response. At this point the patient was given 8 Gm. of ferric ammonium citrate daily for ten days; there was no

12. These lesions are as characteristic of a chronic iron deficiency as they are of riboflavin deficiency, although they have recently been stated to be pathognomonic of the latter.

response to this medication, the hemoglobin concentration being 45 per cent and the red cell count 4,440,000 at the end of the period. The iron was continued, but in addition 20 mg. of copper sulfate was administered daily during the next twelve days. With this regimen, the hemoglobin concentration rose to 56 per cent and the red cell count to 4,300,000. By this time, the patient had gained

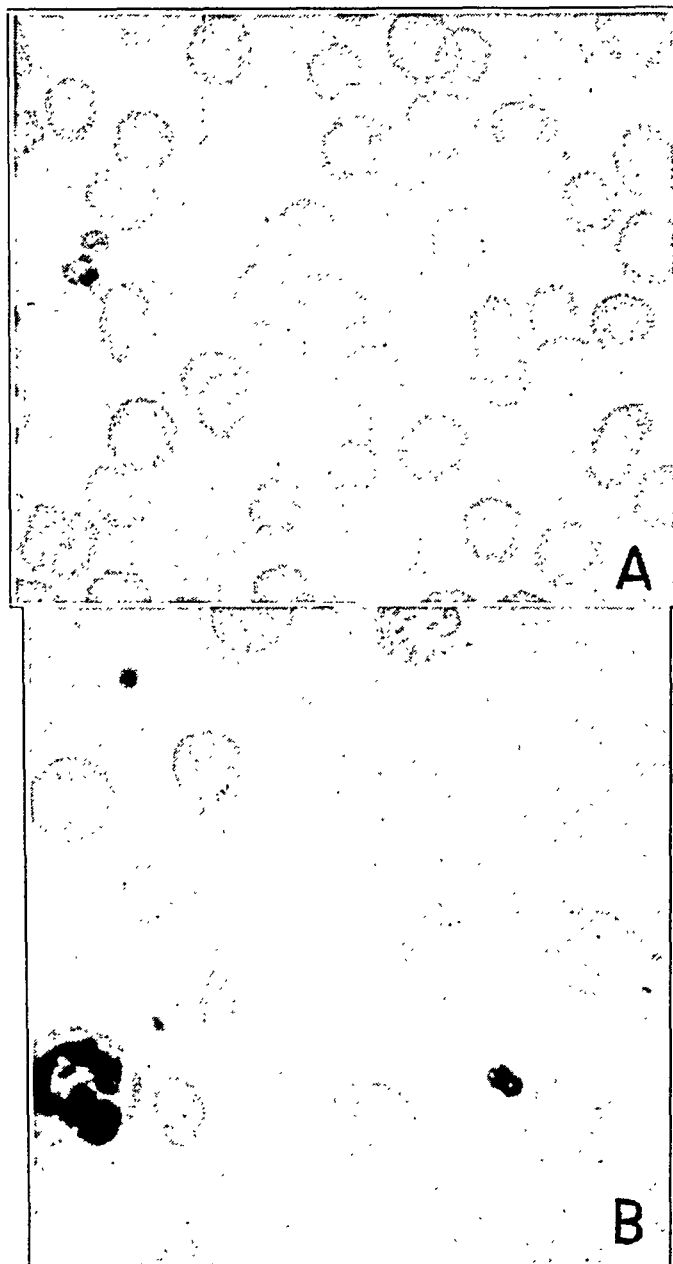


Fig. 1 (case 1).—*A*, photomicrograph of a blood smear ($\times 1,000$) made Jan. 23, 1933 (hemoglobin concentration 23 per cent, red cell count 4,000,000). Note that the red cells are hypochromic and that many are microcytic. *B*, photomicrograph of a blood smear ($\times 1,000$) made April 26, 1939, when pernicious anemia was evident (hemoglobin concentration 34 per cent, red cell count 1,260,000). Note that the red cells are well filled with hemoglobin and tend to be of large size. A granulocyte with a multilobulated nucleus is seen.

8 pounds (306 Kg.) and felt much stronger; the diarrhea had completely disappeared, and the dysphagia had lessened considerably. She was discharged on March 13 on a full house diet, together with 8 Gm. of ferric ammonium citrate and 20 mg. of copper sulfate daily.

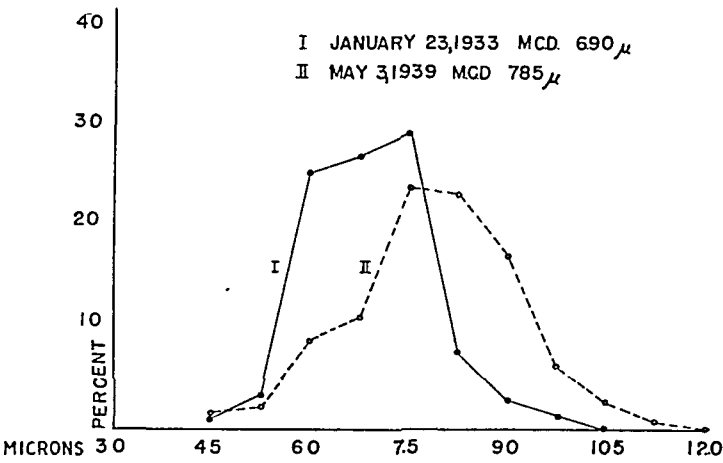


Fig. 2 (case 1).—Price-Jones curves of red cell diameters in the hypochromic (I) and the macrocytic (II) stage. It should be noted that, although the color index in the hypochromic stage is extremely low (tabulation), the erythrocytes which are 7.5 microns or over represent more than 40 per cent of the red cell population. This might indicate a beginning tendency even at this time for the development of macrocytosis (II). *M. C. D.* indicates mean cell diameter.

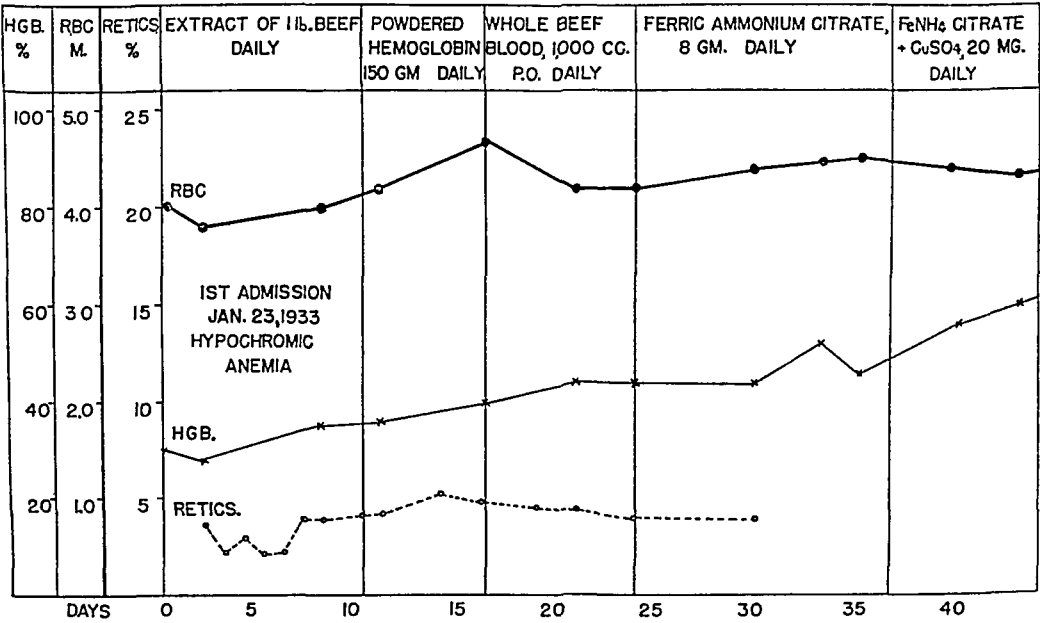


Fig. 3 (case 1).—Hematologic course during the stage of "primary" hypochromic anemia in January and February 1933. There was a slight response to beef extract, powdered hemoglobin and whole beef blood, no further response when large doses of ferric ammonium citrate were given, but a definite response when copper sulfate was added to the iron medication. Note the wide discrepancy between the red cell and the hemoglobin level (low color index).

The patient was seen frequently until September 1933. The red cell count and the hemoglobin concentration remained at about 4,500,000 to 4,800,000 and 60 to 65 per cent, respectively. She continued to feel well and gained weight slowly. The lesions at the corners of the mouth had healed with some scarring, and the nails had lost their vertical striations and flattening and were now completely convex. The dysphagia had lessened considerably, and she was able to eat ground meat despite her dislike for it. The medication was decreased to 5 Gm. of ferric ammonium citrate and 10 mg. of copper sulfate daily. She returned to the clinic in May 1934, stating that she had discontinued her medication during the past eight months. She was eating solid meat and green vegetables once daily, felt well and had continued to gain weight slowly. In October 1934, although she had not taken iron for almost a year, the hemoglobin concentration was 75 per cent. Except for an atrophic tongue, the examination showed nothing significant.

She did not return to the clinic until June 1936. At this time she stated that during the previous six months her symptoms had returned, and there were increasing diarrhea and dysphagia. Examination revealed pallor and a red, atrophic tongue. Neurologic examination showed nothing abnormal. The red blood cell count was now 2,880,000 and the hemoglobin content 71 per cent! One month later examination of the blood showed the red cell count to be 3,220,000, the hemoglobin concentration 77 per cent, the white cell count 6,800, the reticulocyte percentage 1.1, the hematocrit reading 35 per cent, the mean corpuscular volume 109 cubic microns and the average cell diameter 8.10 microns. The icterus index was 10. At this time, the diagnosis of pernicious anemia was made, but when hospitalization was advised the patient disappeared from observation until almost three years later.

Second Admission (May 3, 1939).—During the nine months preceding this admission there had been an increase in the dysphagia and a return of exertional dyspnea, together with swelling of the ankles. The skin had become increasingly pale and more yellowish in appearance. The patient had gradually lost 15 pounds (6.8 Kg.). Because of the dysphagia, she had eaten little meat.

The essential physical findings were as follows: extreme pallor, bilateral posterior cataracts; perforated nasal septum; atrophic glossitis; perlèche at the left side of the mouth; a just palpable liver edge; a systolic murmur at the apex; minimal pitting edema of the ankles; normal finger nails. Vibration sense over the ankles and tibias was diminished, although the reflexes and the gait were normal.

Laboratory Data: Several specimens of urine were normal. Examination of the blood showed: red cells, 1,260,000; hemoglobin concentration, 34 per cent; white cells, 4,400; reticulocytes, 2.0 per cent, and platelets, 270,900. The stained smear showed microcytosis and macrocytosis, and multilobulated leukocytes were present (fig. 1 *B*). Price-Jones diameter curves showed a definite macrocytosis (fig. 2 *II*). The icterus index was 14. Although there was still complete achlorhydria, the gastric analysis now showed essentially normal volumes, as compared with the extremely low volumes recorded several years previously:

Time Elapsed After Injection of 1 Cc. of Histamine Phosphate (Minutes)	Volume, Cc.	Free Hydro- chloric Acid	Total Acid	Lactic Acid	Guaiaec
0 (fasting).....	14	0	6	0	3+
20.....	2	0	0
40.....	71	4	1+
60.....	25	0	3	..	0

Roentgenograms of the gastrointestinal tract showed nothing abnormal, except slight flattening of the greater curvature aspect of the stomach, due apparently to pressure from a slightly enlarged spleen. A sternal puncture showed the typical findings of pernicious anemia, i. e., megaloblastic hyperplasia, with numerous "giant" metamyelocytes.

Clinical Course (fig. 4): In addition to a bland diet, the patient was given tablets of ferrous sulfate in doses of 12 grains (0.78 Gm.) daily for eleven days. At the end of this period there was essentially no change in the blood count; the red cell count was 1,400,000, the hemoglobin concentration 38 per cent and the reticulocyte percentage 4. She was then given liver extract intramuscularly in doses of 1 U. S. P. unit daily for eleven days, after which 6 U. S. P. units of liver extract was given. The peak reticulocyte response was obtained on the twelfth day of liver therapy, when the reticulocyte percentage was 18.

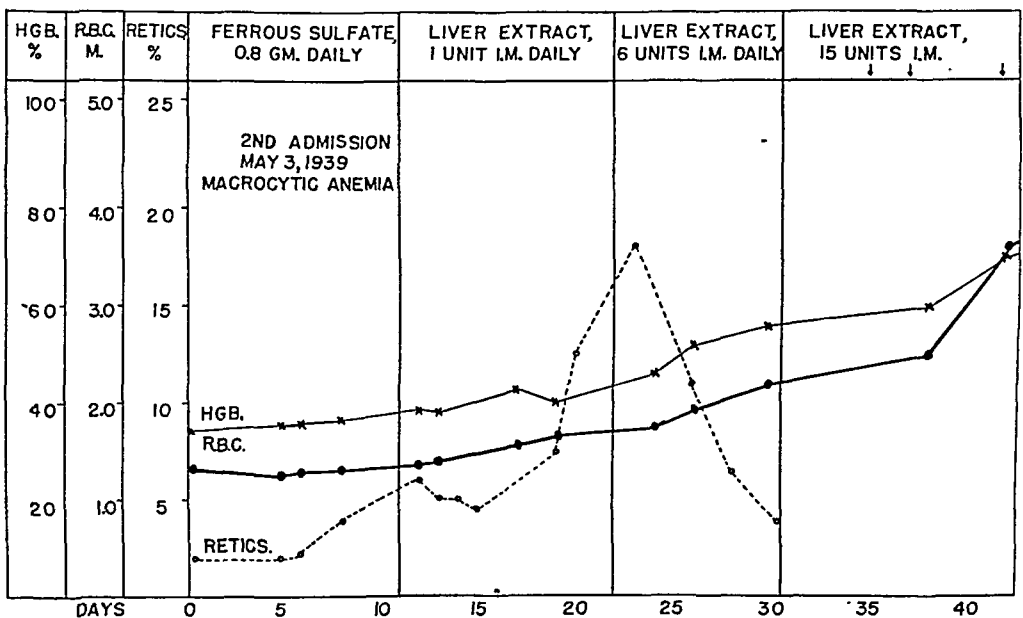


Fig. 4 (case 1).—Hematologic course during the stage of pernicious anemia in May and June 1939. There was a possible slight reticulocyte rise following iron medication, a definite reticulocyte response to 1 U. S. P. unit of liver extract given intramuscularly, followed by a satisfactory erythrocyte increase when larger doses of liver extract were given. Note the high relative concentration of hemoglobin as compared with the red cell count (high color index).

During the next two months, with continued parenteral liver extract therapy, the anemia showed consistent improvement so that on Aug. 4, 1939 the red cell count was 4,550,000 and the hemoglobin concentration was 80 per cent. The patient felt stronger and had gained 5 pounds (2.3 Kg.) in weight. Dysphagia was still present. There was improvement in the vibration sense. The icterus index was 6.

With the continued administration of liver extract, the patient's blood counts have been maintained at normal levels. Dysphagia has continued and has caused great embarrassment in the patient's work as a practical nurse on account of the length of time she requires in eating a meal. Roentgenograms made with a special technic at the Pratt Diagnostic Hospital (Dr. Alice Ettinger, roentgenologist) on

Feb. 4, 1941 revealed two asymmetric indentations of the cervical portion of the esophagus, one about 1 cm. below the other. Above the indentations the passage of the barium meal was somewhat delayed and slight retention was present (fig. 5).

Comment on Case 1.—Course: As a girl, the patient had been sallow and might have been anemic, although this condition is not definitely known to have existed. The chronologic development of symptoms in this case may be tabulated as follows:

Date	Subjective Symptoms	Objective Symptoms	Blood Findings	Diagnosis
Adolescence 1925 (age 32)	Dislike for meat; death of husband; extreme nervous- ness; transitory dysphagia	"Sallow"		
1928 (age 35)	"Tyrannic" em- ployer; severe dysphagia; great limitation of diet; dyspnea; palpita- tion; edema of ankles	Hair beginning to gray; brittle finger nails; red tongue		
1931 (age 32) 1932	Diarrhea; burn- ing tongue increasing symp- toms; paresthesias; scanty catamenia	Pallor	Anemia
1933 (age 40)	Pallor; glossitis; cheilosis; finger nail changes; gray hair; de- layed passage apparent in roentgenograms of esophagus; achlorhydria; small volume of gastric juice; ex- cellent response to therapy with iron and copper	Hemoglobin con- centration 33 per cent; red cell count 4,000,000; color index less than 0.5; mean cor- puscular diameter 6.90 microns	Primary hypo- chromic anemia
1933-1934	Improvement	Atrophic tongue	Hypochromic anemia in remission
1935	Disappearance from observation		
1936	Weakness; diar- rhea; dysphagia	Pallor; glossitis	Hemoglobin con- centration 77 per cent; red cell count 3,220,000; mean corpuscular vol- ume 109 cubic microns	Pernicious anemia
1937-1938	Disappearance from observation		
1939	Weakness; diar- rhea; dysphagia	Pallor; glossitis; subicterus; dimin- ished vibratory sensation; achlorhydria	Hemoglobin con- centration 34 per cent; red cell count 1,260,000; color index 1.35	Pernicious anemia
1939	Improvement (good response to liver extract; no response to iron)	Glossitis	Hemoglobin con- centration 88 per cent; red cell count 4,500,000	Pernicious anemia in remission
1940-1942	Dysphagia	Roentgenographic evidence of "sidero- penic dysphagia"		

In our experience, aversion to meat is a common symptom in cases of both pernicious anemia and "primary" hypochromic anemia. In the case at hand, it appears to have been based on psychic grounds, although occurrence of a similar condition in a niece, as well as the presence of the Plummer-Vinson syndrome

in a cousin, make one suspect a constitutional factor. It is possible that in the presence of achlorhydria there is a greatly reduced craving for meats, which in some cases may develop into an actual aversion.

In most cases of the so-called Plummer-Vinson syndrome (which is simply "primary" hypochromic anemia in association with dysphagia) there is no clearcut history indicating whether the dysphagia antedated the anemic state or vice versa. In the present case, dysphagia first appeared during a serious emotional crisis and grew worse with continued psychic distress. It was followed in due course by severe restriction of solid meat and other iron-containing food and by the symptoms of a deficiency state, namely, diarrhea, glossitis, cheilosis, paresthesias and anemia. It is likely that the constitutional background of achlorhydria and the "psychosomatic" factors just mentioned were probably jointly responsible for the development of the iron deficiency state ("primary," or "idiopathic," hypochromic anemia) which was diagnosed in 1933 and which responded well to the adminis-



Fig. 5 (case 1).—Roentgenogram (reduced) of the upper part of the esophagus taken with thick barium sulfate paste according to the spot film technic. The picture is typical of that obtained in cases of the Plummer-Vinson syndrome and shows two asymmetric indentations in the cervical portion of the esophagus. There are slight delay in the passage of the barium and slight retention above the first indentation.

tration of iron. In 1933, all the typical features of this state, as described by Witts,^{8b} Dameshek,³ Wintrobe and Beebe¹³ and others, were present. These features included considerable sallow pallor without icterus, gray hair, perlèche (cheilosis), atrophic glossitis, complete histamine achlorhydria and probable esophageal changes.

In 1936, however, three years later, the blood picture had become completely modified from that of a hypochromic, microcytic variety of anemia to a hyperchromic, macrocytic type, and the diagnosis of pernicious anemia was made. This was substantiated when the patient continued to relapse and become seriously anemic in 1939. At this time, the bone marrow was megaloblastic; there was failure of response to iron, but there was an excellent response to liver extract.

13. Wintrobe, M. M., and Beebe, R. T.: Idiopathic Hypochromic Anemia. *Medicine* 12:187, 1933.

It appears, therefore, that in this patient there was definite transition from a typical iron deficiency state, with chronic hypochromic microcytic anemia responding to iron, to a typical "liver extract" deficiency state, with chronic hyperchromic macrocytic anemia responding to liver extract. The theoretic implications involved in this transition are of great interest.

The persistence of dysphagia and of the characteristic roentgenographic signs of the Plummer-Vinson syndrome is of some importance. According to Waldenström and Kjellberg,¹⁴ these findings in a case of pernicious anemia may serve as landmarks indicating the previous existence of an iron deficiency state. Anemia is almost always present in the Plummer-Vinson syndrome and, except in 3 recorded instances, has been of the hypochromic type. In the case reported by Croskery,¹⁵ dysphagia was present in association with pernicious anemia; however, the patient was anemic as a girl and, as Waldenström and Kjellberg pointed out, probably had an iron deficiency state at that time. In 2 cases reported by the latter authors, although typical pernicious anemia was present, the serum iron was low, indicating a possible iron deficiency as well. In no previous case of the Plummer-Vinson syndrome has the definite transition from hypochromic anemia to pernicious anemia been recorded. Waldenström and Kjellberg propose the term sideropenic dysphagia for the nondescript term of Plummer-Vinson syndrome.

CASE 2.—Mabel K., a 35 year old housewife, was referred to the Joseph H. Pratt Diagnostic Hospital on Aug. 12, 1940 from the Blood Clinic of the Boston Dispensary, primarily for study of her anemia. She had been weak and tired for many years. Her childhood had been spent in orphanages, where she had never had much to eat. She recalled having taken iron medication in her early years.

She was married at the age of 16, and again at 19, with four resulting pregnancies. Two children were living and well, and the other two died in infancy, of pneumonia and intussusception. Twelve years before admission she was ill for six weeks with abdominal pain on urination and had similar complaints three years later when she was eight and a half months pregnant. Seven years previously, she was advised to take iron because of anemia.

Her diet had been poor for many years. Analysis of the dietary intake revealed that it was high in starches and low in proteins, fats, minerals and vitamins A, C and D and the B complex. It was not unusual for her to go without meat for a month at a time. In addition, her appetite was usually poor, so that the total caloric intake was low and was roughly calculated as 1,500 to 1,600 calories per day.

The menses began at the age of 15 and had always been regular, lasting four to five days. They had never been profuse. During the year before admission they appeared every three weeks and lasted one to six days. Although the presence of hemorrhoids was known, there had never been any grossly bloody or tarry stools. Specific symptoms, such as burning of the tongue, brittleness or spooning of the finger nails, paresthesia of the hands or feet and jaundice or dysphagia were lacking. No history of familial anemia could be elicited.

On admission to the hospital, the patient was found to be underdeveloped and undernourished, weighing but 95½ pounds (43.6 Kg.). The skin was parchment

14. Waldenström, J., and Kjellberg, S. R.: The Roentgenological Diagnosis of Sideropenic Dysphagia, *Acta radiol.* **20**:618, 1939.

15. Croskery, S. E.: Dysphagia Associated with Anemia, *Brit. M. J.* **1**:494, 1928.

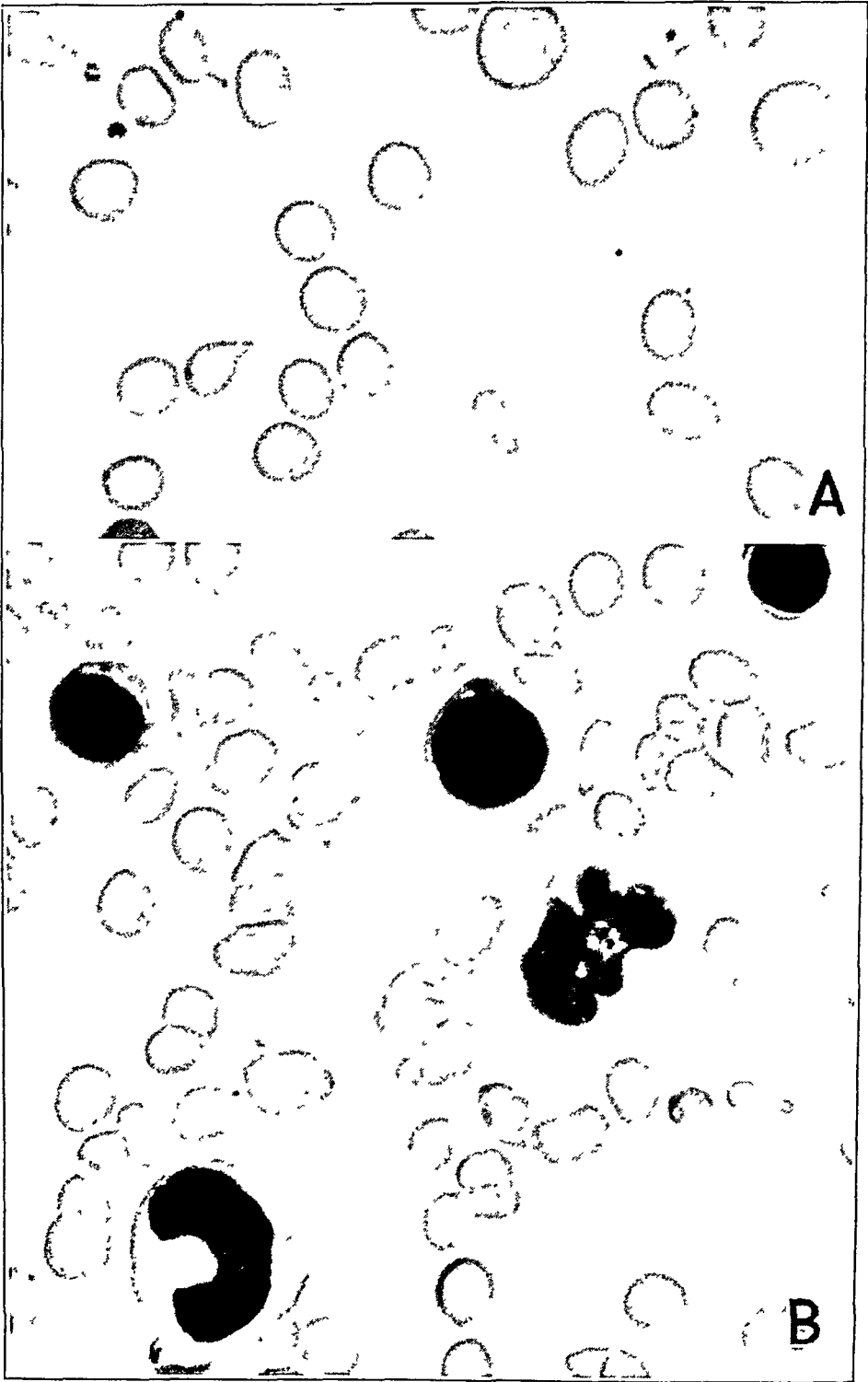


Figure 6

(See legend on opposite page)

pale and without icterus. There was bilateral angular stomatitis (cheilosis), with long reddened fissures about 1 cm. in length, surrounded by scaling skin. The tongue was smooth, glistening and atrophic. The hair and the finger nails were normal. Examination of the heart revealed that the second aortic sound was somewhat accentuated, and the blood pressure was 150 mm. of mercury systolic and 84 mm. diastolic. The liver and the spleen could not be felt. The right knee jerk was somewhat diminished, but the left knee jerk and the ankle jerks were normal; position and vibratory sense were unimpaired.

The laboratory data were as follows: The urine gave a slightly positive reaction for albumin; the sediment showed a few epithelial cells and 3 to 5 leukocytes per high power field. Culture from a catheterized specimen was sterile. The phenolsulfonphthalein test of renal function showed excretion of 64 per cent in two hours. Three stools were negative for ova, parasites and occult blood. The fecal urobilinogen content (daily average output) was 41.2 mg., and the "hemolytic index" was 21.8 (somewhat higher than the usual value, in hypochromic anemia, of less than 10). The Wassermann, Kahn and Hinton reactions of the blood were negative. The blood counts showed: hemoglobin concentration, 38 per cent; red cell count, 2,700,000 per cubic millimeter, and white cell count, 4,300; platelets, 239,000, and reticulocytes, 3.7 per cent. On the smear, the red cells were of two types; most were slightly microcytic and moderately hypochromic, but a few were macrocytic, with a full complement of hemoglobin (fig. 6*A*). The diameters of the red cells varied from 5.3 to 10.5 microns (fig. 7*I*), the average being 6.95 microns. The mean corpuscular volume was 87.3 cubic microns. Gastric analysis showed complete achlorhydria after subcutaneous injection of histamine phosphate.

Time Elapsed After Injection of 1 Cc. of Histamine Phosphate (Minutes)	Volume, Cc.	Free Hydro- chloric Acid	Total Acid	Lactic Acid	Gua'ine
0 (fasting).....	38	0	4	0	0
10.....	3	0	10	0	0
20.....	3	0	5	0	0
30....	3	0	10	0	0
40.....	3	0	15	0	0

Roentgenograms of the gastrointestinal tract were completely normal. Gastroscopic examination revealed a pale mucosa, without evidence of atrophy. In the body on the anterior wall was a localized area, 4 by 5 cm., consisting of convoluted,

EXPLANATION OF FIGURE 6

Fig. 6 (case 2).—*A*, photomicrograph of a blood smear ($\times 1,000$) made Aug. 12, 1940, when the hemoglobin concentration was 38 per cent and the red cell count 2,700,000 per cubic millimeter. Note that, although the cells are generally small and hypochromic, a few definite well hemoglobinized macrocytes are present. *B*, photomicrograph of a bone marrow smear ($\times 1,000$) made Aug. 13. Note the background of hypochromic red cells, the two "giant" metamyelocytes with bizarre nuclei and the three megaloblasts with scanty cytoplasm. Although the anemia was hypochromic, the bone marrow picture was sufficiently like that of pernicious anemia to make one venture the suggestion that a transition to the latter disease might occur.

moundlike patches, each of which measured about 0.5 by 0.5 cm. Puncture of the sternal bone marrow showed the following differential count:¹⁶

Type of Cell	Percentage	Type of Cell	Percentage
Myeloblasts.....	0.0	Erythrogones.....	4.2
Myelocytes.....	9.0	Megaloblasts A.....	5.4
Metamyelocytes.....	2.4	Megaloblasts B.....	14.4
"Giant" metamyelocytes....	23.6	Megaloblasts C.....	9.4
Mature granulocytes.....	8.4	Normoblasts A.....	0.6
Eosinophils.....	0.2	Normoblasts B.....	6.0
Histiocytes.....	0.4	Normoblasts C.....	16.0

The megaloblasts were unusual, not only because of their presence in hypochromic anemia but because of their appearance, for the nuclei were typically "scroll-like"¹⁶ but the cytoplasm was scanty.

The clinical diagnosis was that of hypochromic anemia due to iron deficiency and possibly in some measure to a vitamin B deficiency state. The few following atypical features were, however, present: a normal mean corpuscular volume

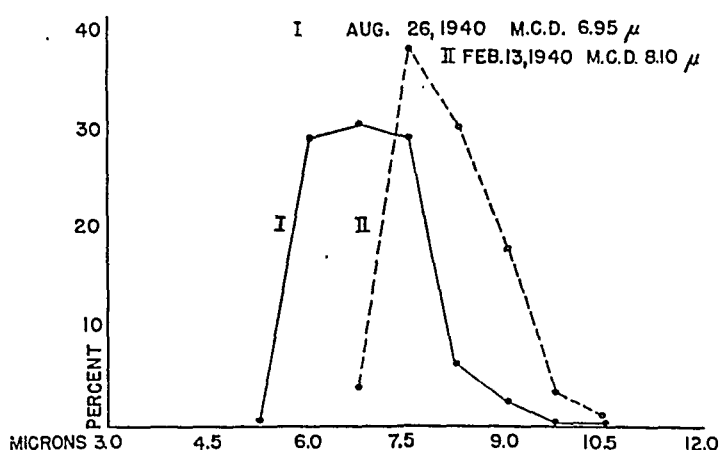


Fig. 7 (case 2).—Price-Jones curves of red cell diameters during the hypochromic, microcytic stage (I) and the macrocytic stage (II). Note the presence of macrocytes during the microcytic stage and the shift to larger cells when iron was given. The iron was apparently responsible for the complete disappearance of the microcytosis (see also figure 9 A).

despite the hypochromia and the low color index; a fair number of macrocytes; the condition of the marrow, which showed bizarre giant metamelocytes and megaloblasts, and the slightly elevated fecal urobilinogen output. Because of these features, the possibility was recorded that the condition might terminate in pernicious anemia.

Clinical Course (fig. 8).—The patient was placed on a diet deficient in vitamin B complex and iron. During the first six days, 10 mg. of riboflavin was given daily by mouth. In two days there was moderate improvement in the lesions at the corners of the mouth; at the end of six days of treatment this improvement was much more noticeable, the lesion on the right being almost completely healed. One gram of ferrous sulfate was then given daily, the use of riboflavin being

16. Dameshek, W., and Valentine, E. H.: The Sternal Marrow in Pernicious Anemia, *Arch. Path.* 23:159 (Feb.) 1937.

discontinued. After nine days the cheilosis was entirely healed, with slight scar formation. During this time there had been practically no change in the blood. The patient was discharged from the hospital on Aug. 27, 1940 and was followed in the blood clinic of the Boston Dispensary.

Continuing to take iron and a full diet including meat three to four times weekly, the patient had gained $7\frac{1}{2}$ pounds (3.4 Kg.) by Oct. 14, 1940 and felt much stronger. Examination of the blood showed the hemoglobin concentration to be 75 per cent, and the red cell count 4,060,000. A seborrheic dermatitis appeared over the malar eminences, and riboflavin (10 mg. daily by mouth) was again given. Despite this medicament, the cheilosis reappeared by the next visit, November 15, and the tongue was still red and shiny. A daily dose of 0.7 Gm. of ferrous sulfate was continued, and nine yeast concentrate tablets daily were

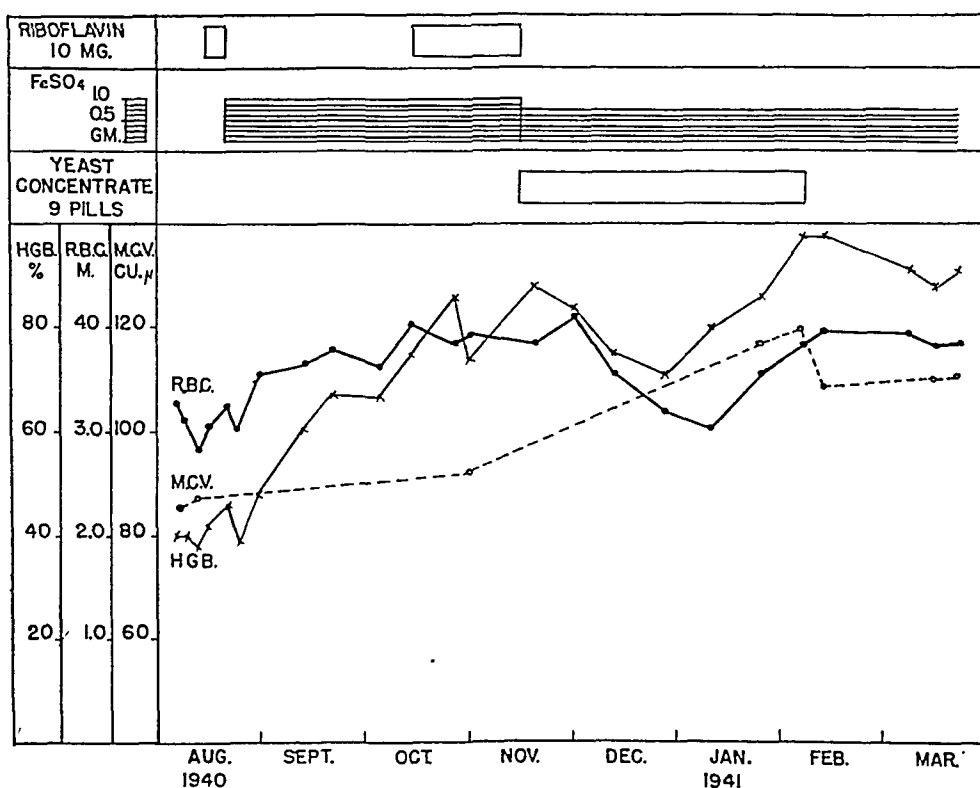


Fig. 8 (case 2).—Hematologic course. Note the relatively low hemoglobin concentration between August and October and the hyperchromia from approximately December to January, with rising mean corpuscular volume (M.C.V.).

substituted for the riboflavin. The cheilosis varied in intensity under this regimen, and the glossitis persisted. In November 1940 it was noted that the slight degree of anemia which was present was somewhat hyperchromic, and by Jan. 10, 1941 the hemoglobin concentration was 86 per cent, the red cell count 3,540,000, the hematocrit reading 42 per cent and the mean corpuscular volume 120 cubic microns. The cheilosis had become worse, despite iron, yeast and a full diet. The blood and bone marrow were carefully restudied on Feb. 13, 1941. Examination of the blood yielded the following information: hemoglobin concentration 98 per cent, red cell count 3,830,000, white cell count 6,900, platelets 440,000, hematocrit reading 46 per cent and mean corpuscular volume 120 cubic microns. The smear revealed hyperchromia and macrocytosis (fig. 9A), the mean cell diameter being 8.2

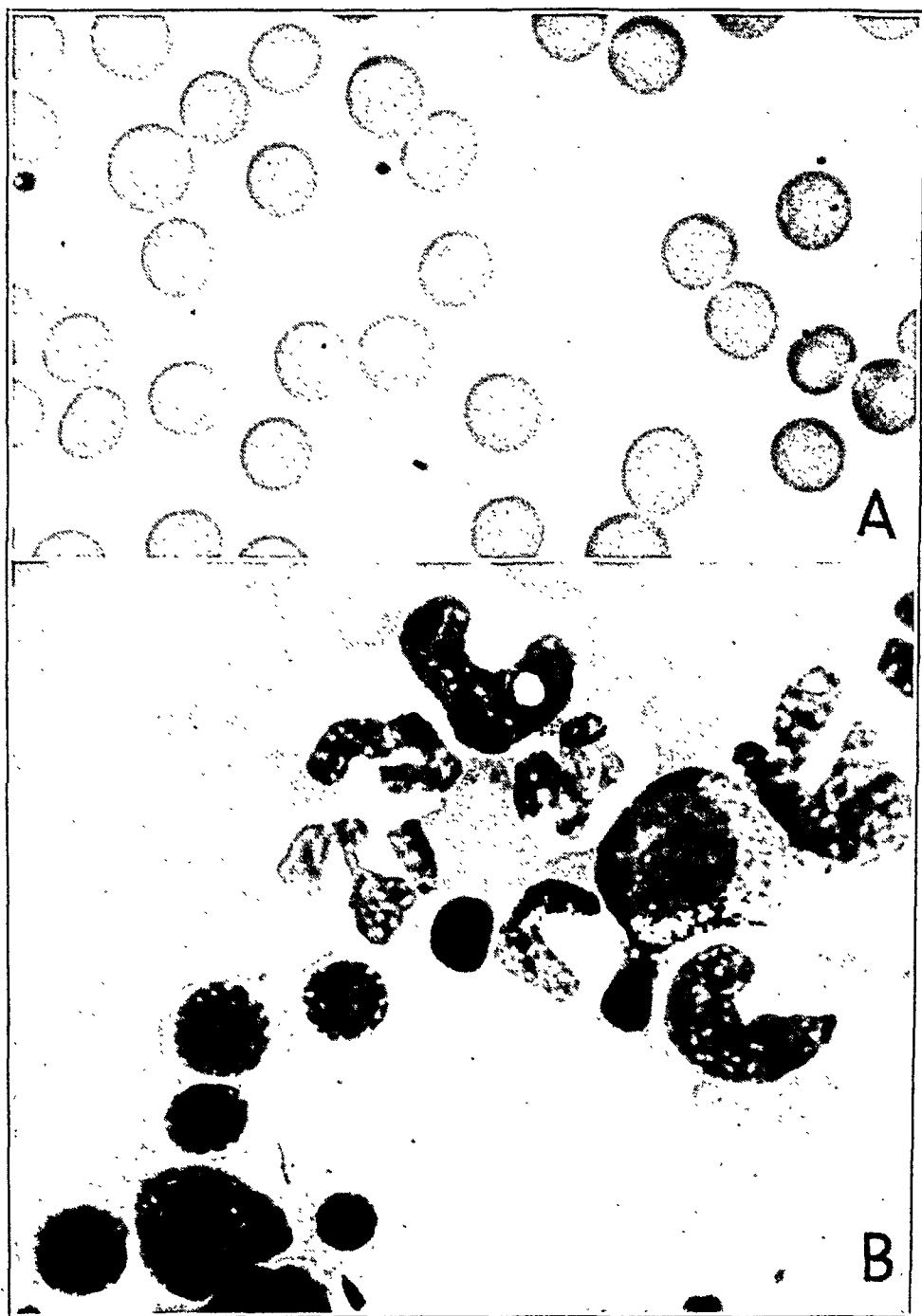


Fig. 9 (case 2).—*A*, photomicrographs of a blood smear ($\times 1,000$) made Feb. 13, 1941 (compare with fig. 7*A*). Note the well defined and uniform macrocytosis and the absence of hypochromia. The complete lack of microcytosis and of hypochromia was probably due to iron therapy. *B*, photomicrograph of bone marrow smear ($\times 1,000$) made Feb. 13, 1941. Note the "giant" bizarre metamyelocytes and the megaloblasts, which are better hemoglobinized than those shown in figure 7*B*.

microns (fig. 7 II). Differential count of smears from the sternal marrow puncture was as follows:

Type of Cell	Percentage	Type of Cell	Percentage
Myeloblasts.....	4.8	Erythrogonos.....	1.4
Myelocytes.....	6.0	Megaloblasts A.....	5.6
Metamyelocytes.....	9.2	Megaloblasts B.....	25.6
"Giant" metamyelocytes....	18.2	Megaloblasts C.....	6.0
Mature granulocytes.....	14.8	Normoblasts A.....	0.0
Eosinophils.....	1.8	Normoblasts B.....	0.2
Histiocytes.....	1.6	Normablasts C.....	0.2
Lymphocytes.....	4.6		

The megaloblasts at this time had their full complement of cytoplasm (fig. 9 B). Gastroscopic examination was repeated, and the observer (Dr. Henry Lerner) noted: "The mucosa was normal throughout, except for an area near the lesser curvature where the light reflex was considerably mottled and the mucous membrane was reddish green."

The patient has no neurologic manifestations and at present shows subsiding cheilosis, mild glossitis, mild hyperchromic anemia with macrocytosis and a bone marrow picture characteristic of a "liver extract" deficiency state. She was placed on a meat-free diet on which she relapsed. She has again been given large daily amounts of meat without liver or kidney. A reticulocyte and erythrocyte response and a great improvement in symptoms indicate a large element of "exogenous" pernicious anemia.

Comment on Case 2.—From the patient's history and the fact that iron was given in childhood and adolescence, it is probable that chronic iron deficiency has been present for many years. In adolescence, "chlorosis" might well have been diagnosed. As probable causes for the iron deficiency, one may list the long inadequate diet, the four pregnancies in rapid succession and a possible constitutional atrophy of the gastric mucosa, with achlorhydria. When first studied by us, the anemia was hypochromic, and the diagnosis of so-called "primary" hypochromic anemia was made because of the appearance of the tongue, the cheilosis, the complete achlorhydria and the absence of bleeding. However, because of a few atypical features—the normal mean corpuscular volume, the presence of some macrocytes, the peculiar appearance of the bone marrow, with bizarre giant metamyelocytes and hemoglobin-deficient megaloblasts, and the slightly increased hemolytic index—the possibility was suspected that this case might be an instance of transition from an iron deficiency state to one of "liver extract" deficiency (pernicious anemia). This possibility eventuated when iron was given in adequate dosage; as a result, the low color index disappeared and was finally replaced by hyperchromia and outspoken macrocytosis.

This case differs from the first one in that it is probable that the two deficiencies—iron and liver extract—were present simultaneously. The administration of iron in this instance did more than relieve a condition of iron deficiency; it "unmasked" a hidden or latent "liver extract" deficiency. The latter deficiency appears relatively mild in view of the almost normal erythrocyte count, the lack of neurologic involvement and the initial and well marked hypochromic character of the anemia. That a "mixed" deficiency is present in other cases of pernicious anemia is not unlikely. Usually, however, the deficiency in iron is slight and is "unmasked" when, following therapy with liver extract, the color index becomes low. Why there is not an outspoken iron deficiency as well in most cases of pernicious anemia is rather difficult to explain, since with an atrophic gastric

mucosa not only is protein digestion interfered with but iron digestion is impaired. It is possible that if one first treated patients with pernicious anemia with large doses of iron and observed the responses, a number of instances of mild iron deficiency would be uncovered. In any event, the existence of a mild pernicious anemia "hiding behind the back" of extreme hypochromic anemia is unusual. The occurrence of such an event makes one suspect that in other cases of primary, or idiopathic, hypochromic anemia, if observation was intensive enough and continued for sufficient lengths of time, the development of macrocytic, hyperchromic anemia of "liver extract" deficiency would be noted.

Relationships of Primary Hypochromic Anemia and Pernicious Anemia.—Castle and his co-workers¹⁷ have shown that the normal gastric juice contains a ferment other than pepsin or rennin, designated as the intrinsic factor, which in the presence of proteins and perhaps the vitamin B complex (extrinsic factor) produces a substance, known as the hemopoietic principle, capable of inducing a remission in patients with pernicious anemia. In a case of typical addisonian pernicious anemia there is an insufficient amount¹⁸ of this ferment. Castle, Heath and Strauss¹ further supported their theory with the demonstration of the presence of the intrinsic factor in cases of achlorhydria without anemia. Singer¹⁹ and Hartfall and Witts²⁰ also found the intrinsic factor present in the gastric juice in cases of simple achlorhydric anemia (idiopathic hypochromic anemia).

Meulengracht²¹ demonstrated that in the pig the intrinsic factor of Castle is produced in the pyloric region of the stomach and in the first portion of the duodenum. The submucous glands of the duodenum are similar histologically to the pyloric glands, and Meulengracht spoke of

17. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am. J. M. Sc.* **178**:748, 1929. Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *ibid.* **178**:764, 1929. Castle, W. B.; Townsend, W. C., and Heath, C. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *ibid.* **180**:305, 1930.

18. Goldhamer, S. M.: The Gastric Juice in Patients with Pernicious Anemia in Induced Remission, *Am. J. M. Sc.* **193**:23, 1937.

19. Singer, K.: Achylie und Anämie, *Klin. Wchnschr.* **11**:1459, 1932.

20. Hartfall, S. J., and Witts, L. J.: Intrinsic Factor of Castle in Simple Achlorhydric Anemia, *Guy's Hosp. Rep.* **83**:24, 1933.

21. Meulengracht, E.: The Glands of the Stomach in Relation to Pernicious Anemia, with Special Reference to the Glands in the Pyloric Region, *Proc. Roy. Soc. Med.* **28**:841, 1935.

them altogether as the "pyloric gland organ." From this evidence it has been assumed that this similarity exists in man also and that in pernicious anemia there is a diffuse atrophic lesion of the stomach also involving the duodenum, which would account for the lack of intrinsic factor in the gastric juice of patients with such disease. Should the atrophic process begin in the proximal half of the stomach, where hydrochloric acid and pepsin are secreted, and then later involve the pylorus and duodenum, as suggested by Hurst,²² a simple explanation would exist for the cases in which primary hypochromic anemia precedes pernicious anemia. A predisposing tendency to atrophy of the stomach, with or without atrophy of the pyloric gland organ, could account for the familial relationship often seen in cases of simple achlorhydria, idiopathic hypochromic anemia and pernicious anemia. In cases of simple achlorhydria a combination of such factors as prolonged iron-poor diet, faulty intestinal absorption and diarrhea, with or without chronic hemorrhage, might finally result in the condition known as "primary," or "idiopathic," hypochromic anemia. There is much clinical evidence in support of the etiologic importance of these various factors. The investigations of Mettier and Minot²³ have suggested that achlorhydria may interfere with the proper absorption or utilization of organic iron. Intestinal malabsorption has also been shown to exist in cases of achlorhydric anemia.²⁴

Magnus and Ungley²⁵ in 7 cases and Meulengracht²⁶ in 8 cases of typical pernicious anemia found a characteristic lesion of the stomach, which was localized to the fundic portion of the stomach and did not affect the pyloric gland organ. Since the glands of the fundus produce chiefly hydrochloric acid, there is a morbid histologic basis for the achlorhydria in pernicious anemia but not for the absence of the intrinsic factor—if one assumes that the latter is produced in the pars pylorus. Magnus and Ungley suggested that the pathologic mechanism in cases of pernicious anemia may be similar to that involving the islets of

22. Hurst, A.: *Observation and Experiment and Physiology of the Stomach*, Brit. M. J. **2**:183, 1937.

23. Mettier, S. R., and Minot, G. R.: *The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia*, Am. J. M. Sc. **181**:25, 1931.

24. Singer, K., and Wechsler, L.: *Klinische Bedeutung und Entstehungsmechanismus des Symptoms: Agalaktosurie*, Wien. klin. Wchnschr. **47**:77, 1934. Heath, C. W., and Fullerton, H. W.: *The Rate of Absorption of Iodide and Glycine from the Gastro-Intestinal Tract in Normal Persons and in Disease Conditions*, J. Clin. Investigation **14**:475, 1935.

25. Magnus, H. A., and Ungley, C. C.: *The Gastric Lesion in Pernicious Anemia*, Lancet **1**:420, 1938.

26. Meulengracht, E.: *Histologic Investigation into the Pyloric Gland Organ in Pernicious Anemia*, Am. J. M. Sc. **197**:201, 1939.

Langerhans in cases of diabetes, in which the lesion is either functional or of an organic type not demonstrable by the histologic technics now available. Meulengracht suggested that the pyloric gland organ may be subject to the influence of a gastric hormone elaborated in the atrophic fundus.

The evidence gained from the literature seems to indicate that some persons possess a constitutional predisposition to gastric achlorhydria, which is often familial. This state need not be associated with anemia or other symptoms. During the stage of simple achlorhydria, hypochromic anemia may result, especially if another factor, such as dysphagia, inadequate diet, intestinal malabsorption or hemorrhage, is present. Occasionally, by an unknown mechanism, the intrinsic factor of Castle may become seriously diminished, with the result that pernicious anemia develops. In our first case, there seems to have been constitutional atrophic gastritis with gastric achlorhydria. During a period of emotion, dysphagia appeared, and because of this difficulty a diet greatly deficient in iron-containing foods was taken. As the result of these various factors, a chronic iron-deficiency state appeared. A few years later, probably as the result of either functional or organic involvement of the pyloric gland organ, the intrinsic factor probably became greatly diminished with the result that pernicious anemia developed.

In our second case, "primary" hypochromic anemia and pernicious anemia were apparently coexistent, although the iron deficiency state was sufficiently outstanding to result in the diagnosis of the first entity. When iron was given, the anemia became macrocytic and the underlying pernicious anemia was "unmasked."

SUMMARY

Two cases of "primary" hypochromic anemia which terminated in pernicious anemia are reported. In the first case, in which the hypochromic anemia was associated with the Plummer-Vinson syndrome, pernicious anemia developed after several years of observation. In the second case, the administration of iron apparently "unmasked" underlying and coexistent pernicious anemia. The possible mechanisms and the theoretic implications of these transitions are discussed.

THE NATURAL HISTORY OF BRONCHIECTASIS

A CLINICAL, ROENTGENOLOGIC AND PATHOLOGIC STUDY

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This study was made in an attempt to trace the natural development of bronchiectasis in a series of cases.

An examination of the voluminous literature yielded much that was helpful, but also much that appeared to be contradictory and confusing. It was felt, therefore, that a fresh start must be made and any conclusions must be based on the continued observation of a number of actual cases. The literature was, therefore, referred to chiefly for the purpose of comparison and for amplification of those aspects which appeared to be inadequately covered by the evidence from the present series.

The subject was a large one, and the method of its treatment was seriously considered. The disadvantages of employing the "textbook" method were realized, but were regarded as capable of exaggeration. No other means of approach can compare with it for comprehensiveness, clarity and ease of reference.

The disease, therefore, was dealt with under the headings of pathogenesis, etiology, clinical features, roentgenologic aspects, classification and prognosis. Treatment was regarded as outside the scope of this article, but the indications as illustrated by this and other series of cases are mentioned in the text. A short section on anatomy and physiology is introduced as a useful preliminary to the study of the abnormal condition.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Bronchial Tree.—The mode of branching of the bronchial tree has been a subject of controversy, and a dissection of a normal lung was therefore made. From this dissection it became clear that bronchial branching is monopodial as far as the finer bronchi, i. e., the smallest capable of gross dissection. Dichotomy then becomes the method of choice, and Willson¹ stated that this is followed as far as the alveolar ducts, except where it conflicts with the overriding law of the economy of space, which is rigidly observed.

This paper represents the substance of an essay accepted for the degree of Doctor of Medicine at the University of Durham, Durham, England.

1. Willson, H. G.: *Am. J. Anat.* **30**:267, 1922.

The various lobular areas which have been described as likely to form supernumerary lobes were readily recognized. With the exception of the lingular lobe, no instances of supernumerary lobes were confirmed at operation or autopsy in the present series, although such lobes are generally regarded as peculiarly liable to the development of bronchiectasis.

The normal bronchial structure is of the utmost importance in any study of abnormal bronchi, and a brief account of the salient points is therefore given.

The bronchi are to be regarded as tubes of muscular and elastic tissue, the "myo-elastic" tissue of Macklin,² which are enclosed in a sheath of collagen and elastica, stiffened by cartilaginous plates and lined by a continuous sheet of epithelium. The arrangement of this "myo-elastic" tissue is most important. Internally, beneath the mucosa, is a layer of branched elastic fibers, which is succeeded by flat, branching muscular bundles, among which run numerous elastic fibers. The muscle is loosely packed, with angular spaces between the bundles, and is thus arranged in the form of a branching network. The elastic fibers run parallel to the muscle strands. Macklin described the arrangement as a "branched tubular net." This association of muscle and elastic tissue becomes even more intimate as the finer bronchial tubes are reached, and the tunica propria disappears as a separate layer. The muscle of the bronchi, although the direction of the fibers varies from point to point, is neither circular nor longitudinal, but rather oblique. Miller³ used the term "geodesic network" suggested by Max Mason. It is of interest to note that the fuselage of the new Wellington bomber is constructed in a somewhat similar fashion.

Miller's description of the bronchial blood supply is classic and well known, and it is not proposed to do more than to point out how liable is the internal capillary network to hemorrhage in destructive lesions of the tubes.

There is general recognition of the fact that the bronchi play an important part in respiration and are not mere passive conducting channels. During inspiration the bronchial muscle relaxes, and, owing to the arrangement of the myoelastica, the tubes widen and elongate. Their narrowing and shortening again on expiration is due to active contraction of the muscular and natural recoil of the elastic tissue. Muscle and elastica act evenly and harmoniously together.⁴ Ingals⁵ and Jack-

2. Macklin, C. C.: *Physiol. Rev.* **9**:1, 1929.

3. Miller, W. S.: *The Lung*, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

4. Willson.¹ Macklin.²

5. Ingals, E. F.: *Respiratory Movements of the Bronchial Tubes*. *J. A. M. A.* **45**:1302 (Oct. 28) 1905.

son⁶ observed these movements through the bronchoscope, and general agreement thus far appears to have been obtained. The work of Bullowa and Gottlieb⁷ and of Hudson and Jarre⁸ was also of importance in this connection.

Is this change in capacity, together with ciliary action, the whole story of bronchial function? Horvath⁹ and von Schrotter¹⁰ described a peristaltic movement of the bronchi, but little attention seems to have been paid to their views for some years. Bullowa and Gottlieb⁷ and Reinberg¹¹ revived interest in the question. These workers observed waves of peristalsis 10 cm. in extent, when radiopaque material was

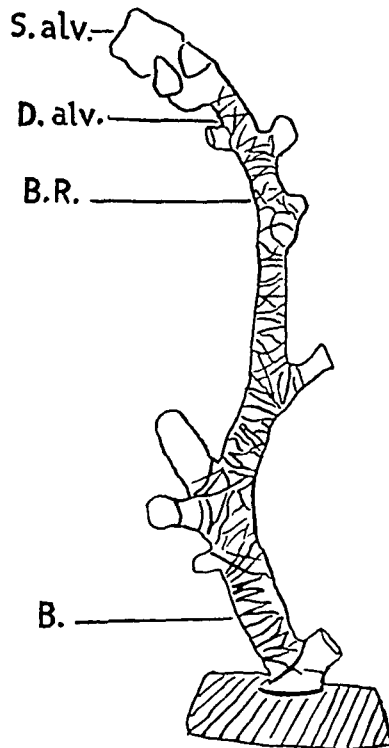


Fig. 1.—Model of a noncartilaginous bronchiole from a dog's lung, showing the muscular arrangement when the bronchiole is in a condition of full inspiration. *B.*, bronchiolus; *B. R.*, bronchiolus respiratorius; *D. alv.*, ductulus alveolaris; *S. alv.*, sacculus alveolaris (Miller³).

introduced into the bronchi. Reinberg made his observations on a patient with paralysis of the recurrent laryngeal nerve and described the phenomenon as "tracheal vomiting." These movements could be differen-

6. Jackson, C.: *Bronchoscopy and Esophagoscopy*, ed. 2, Philadelphia, W. B. Saunders Company, 1927; *Tr. Am. Laryng. A.* **40**:319, 1918.

7. Bullowa, J. G. M., and Gottlieb, C.: *Am. J. M. Sc.* **160**:98, 1920; *Laryngoscope* **32**:284, 1922.

8. Hudson, W. A., and Jarre, H. A.: *Grace Hosp. Bull.* **13**:15, 1929.

9. Horvath, A., cited by Reinberg.¹¹

10. von Schrotter, cited by Reinberg.¹¹

11. Reinberg, S. A.: *Brit. J. Radiol.* **30**:451, 1925.

tiated from transmitted impulses and were independent of coughing, which either hastens the centrifugal movement of material or "splashes it peripherally." Jackson was unable to confirm bronchial peristalsis, but probably the bronchoscope is not the best means of observing such a phenomenon. Ellis¹² pointed out that records from two fixed points in the same bronchial tube are required for proof that the evidence is at least strongly suggestive. Macklin summed up the evidence by saying that peristalsis is probably slight under normal conditions but plays the major part in the expulsion of secretions and foreign bodies.

The presence of abundant sensory nerve endings in the bronchial wall and the existence of Remak's ganglion show that an apparatus for peristaltic action exists. It appears that the bronchi have a passive role in inspiration, but that in expiration the active contraction of the myo-elastic tissue plays an important part. In the expulsion of secretions and foreign material from the lung the ciliary action and probably bronchial peristalsis are together responsible for shepherding these substances to a point whence they may be expelled by coughing.

Air Sacs and Alveoli.—Little need be said on this subject. The chief, if not the only pertinent, feature of the alveolar arrangement is the relation of the air cells to the bronchi. This is in reality complex, but it is unnecessary to go into detail here. All intrapulmonary bronchi are completely surrounded by air cells. The bronchial system is thus strengthened and supported by a vast and most efficiently disposed air cushion, consisting of no fewer than 725,000,000 minute but inflated alveoli. It will be readily appreciated that a condition of atelectasis will deprive the tubes of this support and render them liable to dilatation.

PATHOGENESIS

ACQUIRED BRONCHIECTASIS

A discussion of the numerous theories is both unnecessary and likely to prove tedious, if not confusing. Ballon, Singer and Graham¹³ recently studied the matter exhaustively, and reference to their monograph is suggested. All the possible causes of bronchiectasis which have been mentioned in the literature can, moreover, be grouped under two headings:

1. Defects in the bronchial wall.
2. The various stresses and strains to which the bronchial wall may be subjected.

Defects in the Bronchial Wall.—Acquired bronchial defects have been stated to be due to damage caused by infective processes or by

12. Ellis, M.: *Lancet* 1:819, 1938.

13. Ballon, H.; Singer, J. J., and Graham, E. A.: *J. Thoracic Surg.* 1:154, 1931.

inorganic substances, such as silica and poisonous gases. A contributory factor which has been emphasized by Ameuille and Lemoine¹⁴ is interference with bronchial nutrition by vascular disease of the bronchi.

The extraordinary efficiency of the myoelastic tissue, which has already been described in some detail, indicates that serious weakening of the wall can be produced only by actual destructive changes, which must extend to the deeper layers. Minor localized areas of damage are, by themselves, insufficient to produce it, although extensive inflammatory changes short of destruction may interfere with bronchial function sufficiently to favor the maintenance of an infective process and to reduce bronchial elasticity.

The first step must, therefore, be to examine the available evidence as to the actual condition of the bronchial wall in bronchiectasis. It is preferable that this evidence should be based on the study of "living" lobes rather than of postmortem material, for obvious reasons, but the relatively recent expansion of the scope of lobectomy limits the possibilities of this method. The only pathologic studies of lobes removed at operation which I have been able to review are those made by Robinson¹⁵ and Goodman,¹⁶ the work of Sauerbruch¹⁷ and the report on lobes studied at Brompton Hospital, given by Lander and Davidson¹⁸ in their recent article.

Robinson examined 16 lobes excised by Janes from 10 patients. He found as the outstanding and most consistent observation a "chronic inflammatory condition of the bronchial walls with various degrees of damage up to complete destruction of the musculo-elastic tissue." He visualized early paresis of the muscle, due to infection, which leads to dilatation. At this stage, he stated, recovery may occur, but with persistent or more severe infection permanent damage results. This change, in its turn, favors further persistence of infection, and a vicious circle becomes established. He found no evidence of significant collapse or pleural adhesions in his patients.

Goodman was emphatic as to the pronounced changes in the bronchi and peribronchial tissue, although he did not give details. He said:

The pathological features of all these cases was very impressive. The lobes in all cases were markedly adherent to surrounding structures in the chest. There was considerable induration throughout the lobe with very little crepitation noticeable. On section they all showed markedly dilated and thick-walled bronchi. The tissue around the bronchi appeared hepatized, hemorrhagic and in some cases undergoing suppuration.

He also mentioned the purplish blue to dark slate color of the lobes.

14. Ameuille, P., and Lemoine, J. M.: *Presse méd.* **43**:873, 1935.

15. Robinson, W. L.: *Brit. J. Surg.* **21**:302, 1933.

16. Goodman, H. I.: *Am. J. Surg.* **26**:543, 1934.

17. Sauerbruch, F.: *Chirurgie der Brustorgane*, Berlin, Julius Springer, 1929, vol. 1, pt. 1, p. 869.

18. Lander, F. P. L., and Davidson, M.: *Brit. J. Radiol.* **11**:65, 1938.

Sauerbruch described two types of bronchiectasis, "congenital" and "inflammatory." The "congenital" type will be considered at the end of this section, but it may be stated here that he expressed the opinion that it is to be found in all children in whom bronchiectasis is confined

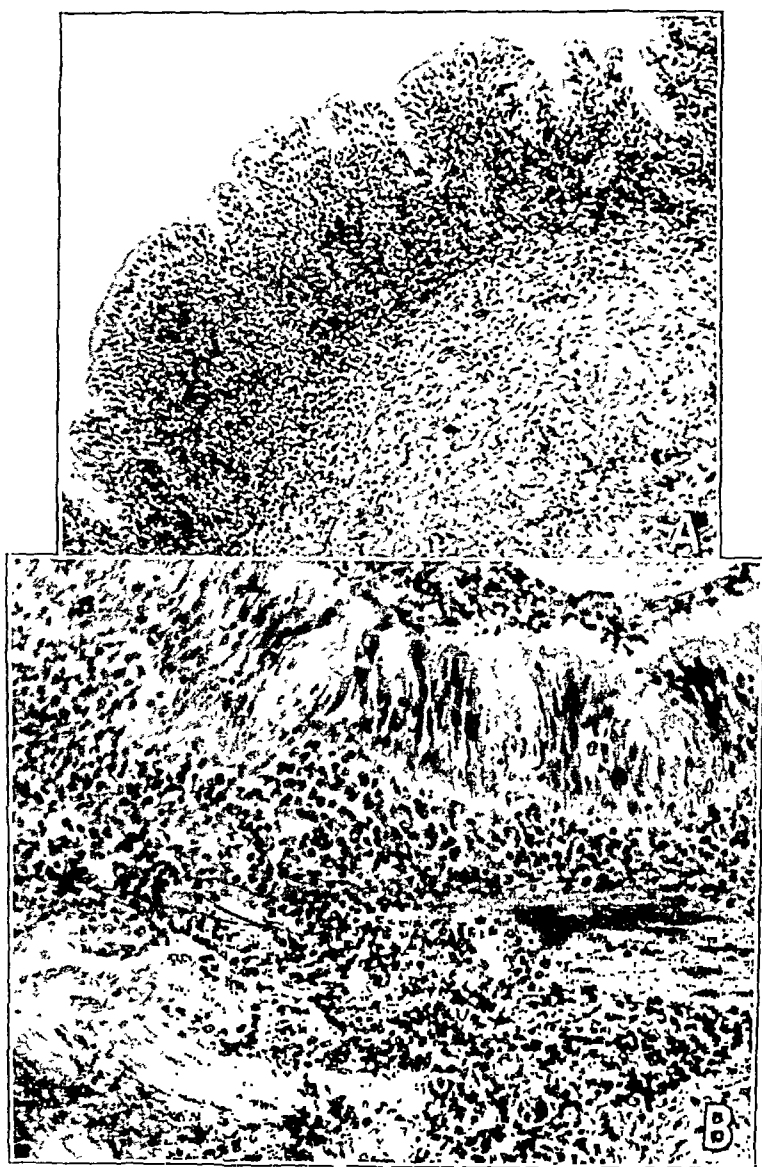


Fig. 2.—A, "inflammatory infiltration of the subepithelial layer"; B, "degenerative changes in muscle fibers and some splitting of the elastic lamellae are shown." ¹⁵

to one lobe and that the lobe thus affected is atelectatic. Pleural adhesions are absent. In the "inflammatory" type the position and sequence of the layers in the bronchial wall are clearly discernible, but the muscle and elastic fibers are split up. There are metaplasia of the epithelium

and resorption, and even calcification, of the cartilage. Granulations "spring up" in the diseased areas (and may lead to hemorrhage which is evident clinically). If obstruction is present even the neighboring pulmonary tissue may be destroyed. Sauerbruch remarked that in this type more than one lobe is usually affected, and did not mention atelectasis as a feature.

Evidence of infection was clear in both these accounts, but it is rather difficult to explain the slight degree of bronchial damage which Sauerbruch seemed to indicate is associated with destruction of the surrounding pulmonary tissue. Furthermore, the granulations which "spring up" clearly indicate a destructive change.

Lander and Davidson were more emphatic as to the minimal bronchial damage which may be observed. They stated that examination of 140 lobes removed from patients at the Brompton Hospital showed that infection was negligible in those specimens. "A histological study . . . shows not only an intact mucous membrane, very often ciliated, . . . but also the presence of all the normal layers of the bronchial wall." The only exceptions to this observation were found in sections taken through saccules, which showed epithelial lining and fibrous tissue only and were always peripherally situated. The authors expressed the opinion that they were "probably caused by the extreme dilatation of minute bronchi and bronchioles, which normally contain no glands, no cartilage, and a minimal amount of muscle." Pleural adhesions were exceptional in their specimens, they said, while the lobes were collapsed to a greater or lesser extent. There was no mention of any bronchial destruction, such as Robinson described, or of any granulations, such as Sauerbruch mentioned. Such a conflict of experience is disconcerting and is difficult to explain as coincidental.

A study of the pathologic features of the present series, therefore, seemed the most obvious step, and the following account is a summary of the results of this study.

Lobectomy was performed in 35 cases. Excised lobes from patients in 28 of these cases, comprising 35 specimens, were available for study.

A. Macroscopic Appearance: Comment will be limited to an account of the condition of the pleura and of the general appearance of the parenchyma.

The condition of the pleura is of interest in view of the statements as to the prevalence of a normal pleura in bronchiectatic lobes. It was found easy to divide the specimens into two groups: those in which gross thickening was associated with the presence of stout tags representing divided adhesions, and those in which changes were moderate or absent.

The pleura was much thickened in 25 specimens, while pleural changes were minor in only 10 specimens. These figures do not lend support to the view that pleural changes are usually slight or absent.

The general appearance of the parenchyma and the actual size of the excised lobe or lung were studied because sections of a whole lobe were available in only a minority of the cases. Small sections gave a less satisfactory idea of the condition of the lobe as a whole, and the appearance to the naked eye was helpful on this account.

The specimens were divided into three groups on a second basis: those in which collapse was really extensive, or apparently complete; those in which collapse was patchy or local, and those in which collapse appeared to be negligible. In the tabulation which follows, these groups are shown in relation to the size of the lobe and the presence of parenchymal scarring and emphysema, which was regarded as probably compensatory.

Collapse	No. of Specimens	Size of Lobe	Scarring of Parenchyma	Emphysema
Extensive	22	All shrunk	10	6
Local or patchy.....	9	All normal	4	8
Negligible	4	All normal	1	4

The high proportion of specimens showing extensive or apparently complete collapse is noteworthy, as is the fact that in all of these the lobe was definitely shrunk. Apparent parenchymal scarring was noted in more than one third of the specimens. No further comment seems necessary.

B. Microscopic Examination: Histologic sections of 31 specimens were available for study. For a minority of these specimens sections of the whole lobe or the whole lung were available, and for the others there were smaller sections only.

Particular attention was paid to the condition of the bronchial wall and to any evidence of inflammation or damage which it might present. In addition, the parenchyma of the lung was studied, and the state of the vessels, the lymphoid tissue and the bronchial mucous glands was noted. Conditions varied in different specimens and in different parts of the same specimen.

In the majority, however, more or less severe bronchial destruction was evident, and all showed well marked inflammatory changes.

The condition of the parenchyma varied, also, but the preponderance of extensive pulmonary collapse, noted in the foregoing account of the macroscopic appearance, was confirmed. Other parenchymal changes were patchy or confluent bronchopneumonic consolidation and emphysema. Emphysema was noted in all specimens and varied from small patches to extensive areas, even in specimens in which collapse appeared complete on gross inspection. This last observation was interesting and rather unexpected, as little or no mention of emphysematous areas was

made in the literature and from accounts of "atelectasis" one gained the impression that collapse is complete.

Endarteritis was noted in all specimens, and in many it was gross and widespread. Lymphoid hyperplasia was conspicuous throughout, and in most specimens a pronounced increase in the number of bronchial



Fig. 3.—Specimen from lobectomy; actual size. The bronchiectasis was of the bronchopneumonic type. The patient was a child of 13.

mucous glands was noted. The latter changes were regarded as important, because they are so typically associated with inflammation of long standing.

For purposes of more detailed description, it was found convenient to divide the specimens into two groups on a third basis.

1. Specimens in which pulmonary collapse was extensive, the "atelectatic" group: This group comprised 21 specimens.

The bronchial lining was usually complete, although in places a break in continuity was observed. The lining was composed of columnar and squamous epithelium, and in most bronchi the transition from the one to the other was seen. Cilia were rarely observed. Certain of the



Fig. 4.—Specimen from lobectomy; actual size. The bronchiectasis was of the atelectatic type. The patient was a child of 12.

bronchi were lined completely by columnar or by squamous epithelium, as the case might be, but these were in the minority. A feature of the squamous epithelium was its tendency to be heaped up into layers.

The lumens of the bronchi were frequently stellate in cross section, giving an appearance which has been recorded in the literature and has been variously interpreted. Opie expressed the opinion that it was due to splitting of the bronchial wall in certain places, with subsequent sealing by scar tissue. Bronchial inflammation was easily apparent in all specimens, but wide variations in the condition of the wall were seen.

All grades of inflammation were observed, from the presence of a complete muscle layer and absence of scar tissue to more or less complete replacement of the bronchial structure by organizing granulation tissue showing evidence of scarring.

In some specimens the majority of bronchi were relatively normal, though inflamed, whereas in others most of them were extensively damaged. Some bronchi occupied a roughly intermediate position. In general, the cartilage did not appear to be grossly affected.

Eleven specimens (52.5 per cent) showed evidence of severe destruction. Eight specimens (38.0 per cent) showed evidence of more moderate destruction and 2 specimens (9.5 per cent) evidence of slighter damage. It is clear that bronchial destruction was, on the whole, a prominent feature in these specimens.

Along with bronchial inflammation were noted changes in the vessels in the form of endarteritis, hyperplasia of the lymphoid tissue and increase in the number of mucous glands.

The granulation tissue, which in cases of severe damage replaced the normal bronchial structure, was typical and highly vascular, with the new vessels directed toward the surface and with fibers of young scar tissue running through it like a skein.

The parenchyma was, as has been indicated, extensively collapsed, but in no case was this collapse complete and in a few was far from being so. In sections of a whole lobe the emphysema was usually seen as strips of varying width occupying the periphery of the section, but in 1 case the central portion was emphysematous and the remainder collapsed. In the case of 1 specimen doubt was felt as to its proper inclusion in this group, owing to the degree and extent of emphysema. It was considered, however, that the extreme distention of the emphysematous area exaggerated its true extent, considered in terms of lung area.

Patches of emphysema were noted, also, to be scattered here and there through the central part of the sections.

It is thus evident that collapse is far from complete even in lobes which are solid and shrunken and which are dense enough to produce a typical "atelectatic" shadow in a roentgenogram.

Parenchymal scarring was evident in varying degree in 10 specimens, but was mainly peribronchial. Patches of bronchopneumonia were occasionally seen, but were inconspicuous.

2. Specimens in which collapse was patchy or negligible, the "bronchopneumonic" group: This group comprised 10 specimens, 8 (80 per cent) of which showed evidence of severe destruction and 2 (20 per cent) evidence of moderate destruction.

In all 10 specimens scarring of the parenchyma was evident. The number was small, but there was a suggestion of rather more severe bronchial damage in this group, which was called the bronchopneumonic group on account of the prominence of patchy or confluent broncho-

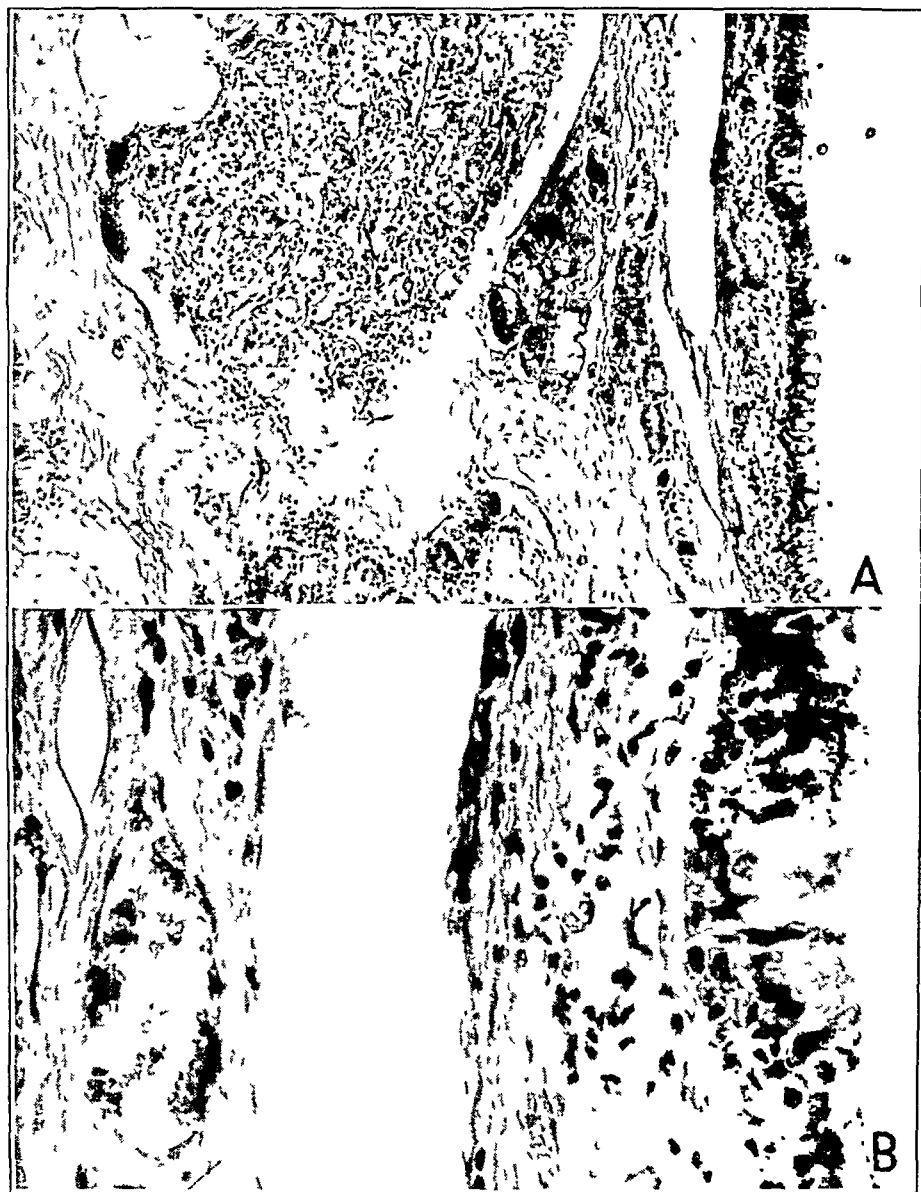


Fig. 5.—*A*, wall of a normal bronchus; $2/3$ power lens. Note the normal arrangement of epithelium and muscle tissue and the presence of mucous glands and vessels. *B*, a portion of the wall more highly magnified to show its structure in detail; $1/6$ power lens.

pneumonic consolidation and of parenchymatous scarring and the relative absence of collapse.

The histologic appearances of the bronchi presented no striking qualitative differences from those already described in the atelectatic group. Endarteritis and lymphoid hyperplasia were conspicuous. The parenchymal changes differed considerably.

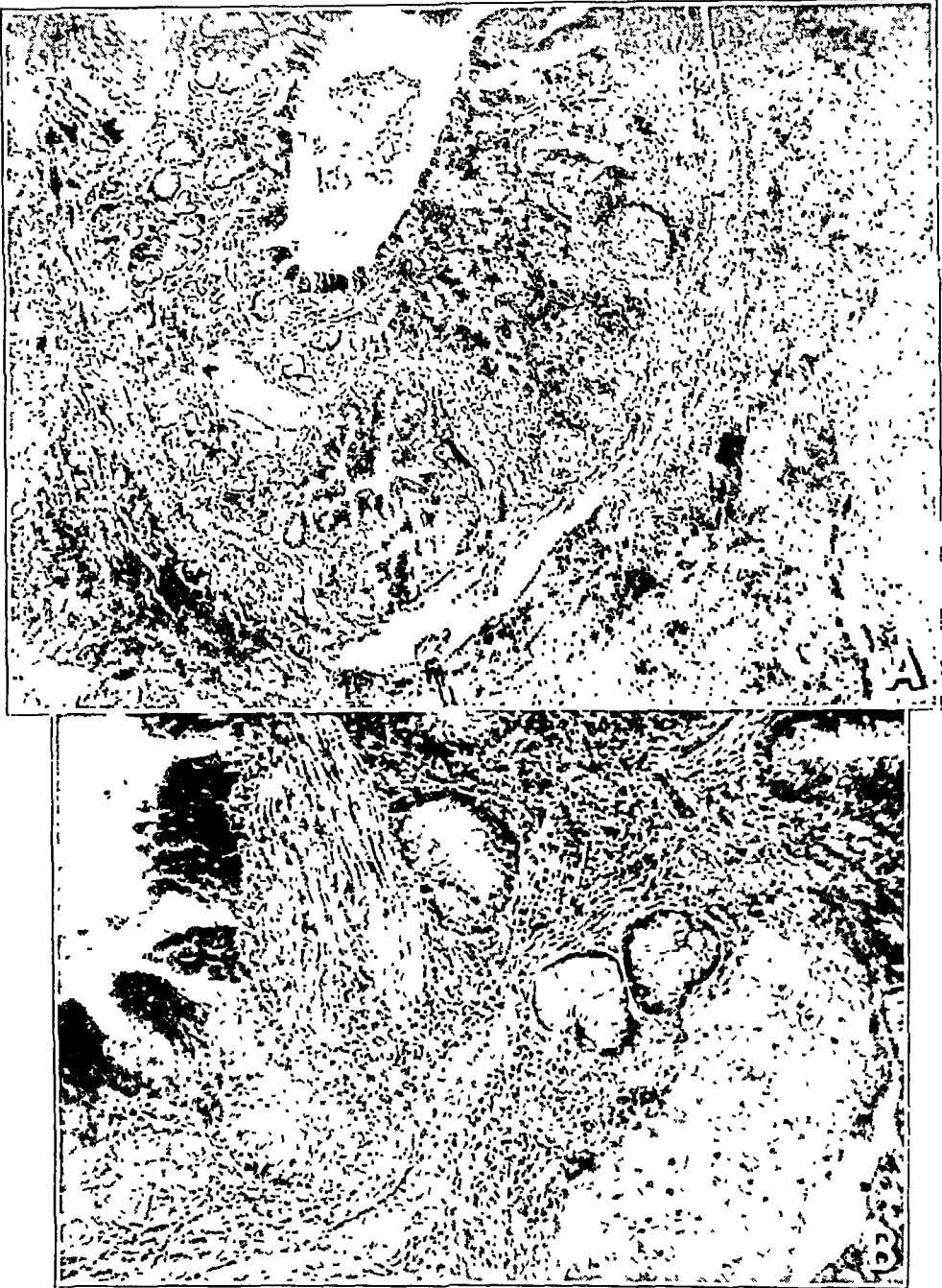


Fig. 6.—Atelectatic bronchiectasis. *A*, a section through a portion of diseased lung shows collapse of the parenchyma, hyperplasia of lymphoid tissue and excess development of mucous glands; 2d power lens. *B*, a portion of the section is more highly magnified to show the wall of the chief bronchus in detail. Note that the muscle is in a fairly good state of preservation but that inflammation is evident. Granulations, containing new blood vessels and a few strands of scar tissue, are present. 2/3 power lens.

Patches of collapse were noted in some sections, but in none were they a prominent feature. For the most part, patchy or confluent consolidation, peribronchial in distribution, alternated with areas of

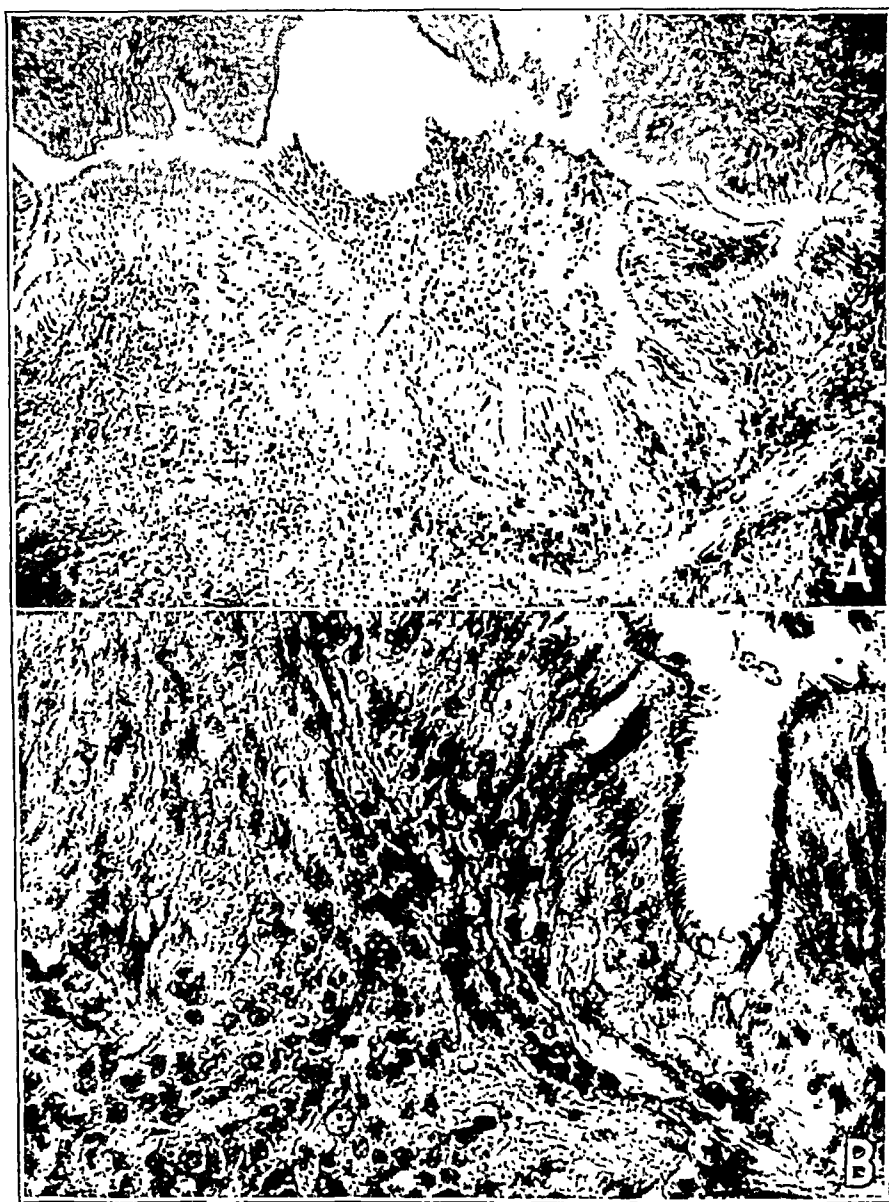


Fig. 7.—In *A*, from another case of atelectatic bronchiectasis, the bronchial damage is much more extensive. The wall is composed chiefly of highly vascular granulation tissue. Note the numerous young blood vessels. There is definite evidence of organization; “skeins” of scar tissue are present; muscle is scanty. $2/3$ power lens. In *B*, a more highly magnified portion of the bronchial wall, a muscle bundle is visible, but is undergoing degenerative change. Granulation tissue is obvious. There is a break in the continuity of the columnar epithelium at one point, but multiplication of the basal cells to repair the break is taking place. It is noteworthy that ciliated columnar epithelium lines such an abnormal bronchus. Obviously, this is the result of a regenerative process. $1/6$ power lens.

emphysematous or air-containing pulmonary tissue, and evidence of destructive pulmonary changes was noted in a few areas.

Comment: It appeared from this pathologic study that bronchiectatic lobes removed from living patients commonly show pronounced changes.

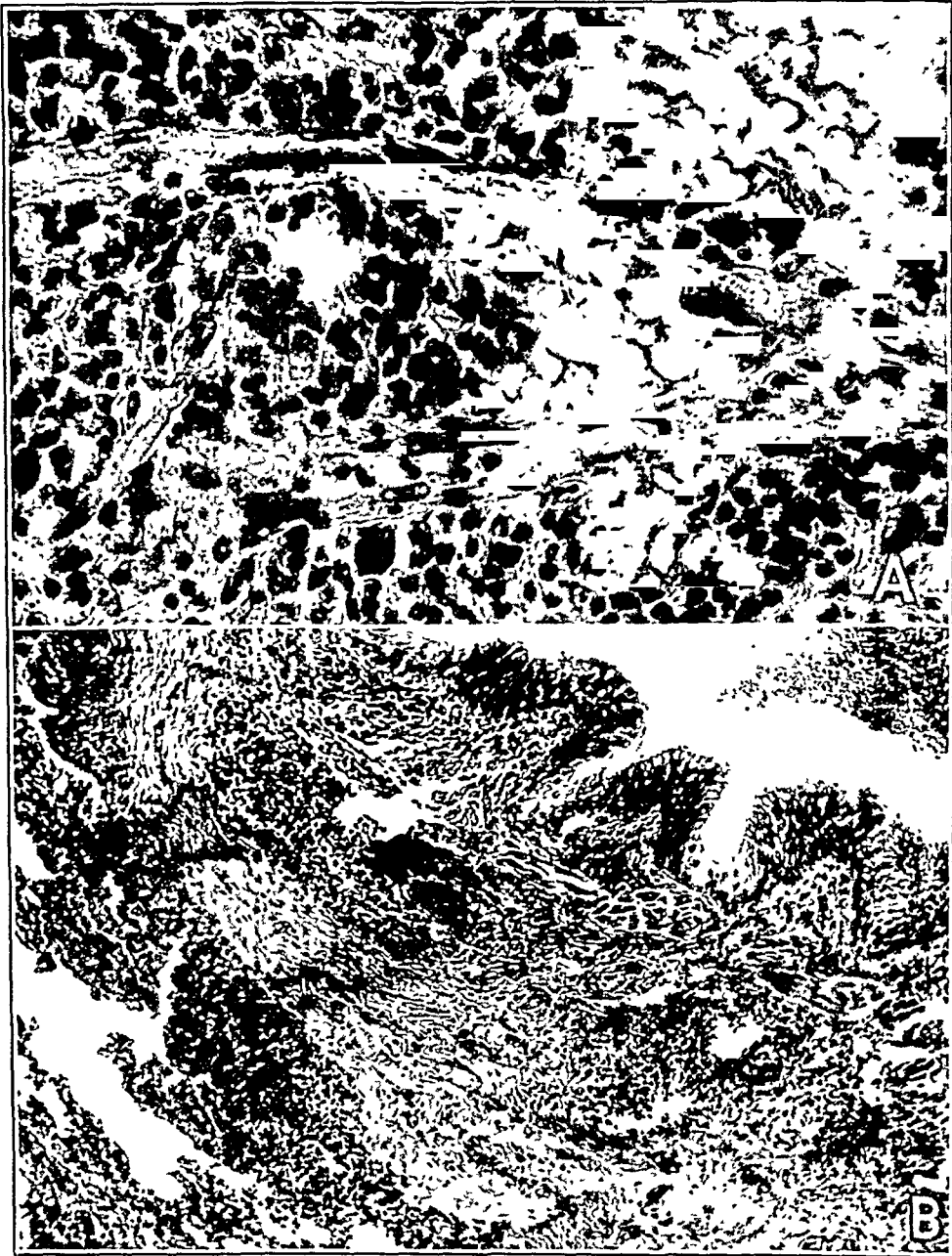


Fig. 8.—*A*, granulation tissue and formation of new vessels in the bronchial wall; 1/6 power lens. *B*, inflammation of the bronchial wall and peribronchial scarring. The bronchial muscle is well preserved. 2/3 power lens.

Not only was considerable inflammation a prominent feature, but actual destruction of the bronchial wall was frequently found. Those other changes which are to be expected in association with chronic

bronchial inflammation of any severity were observed. These were endarteritis, lymphoid hyperplasia and hypertrophy of mucous glands.

Brock¹⁹ recently emphasized the pronounced changes in lymphoid tissue seen at operation. He said that "the importance of the lymph glands . . . is constantly forced upon one in lobectomy for bronchiectasis

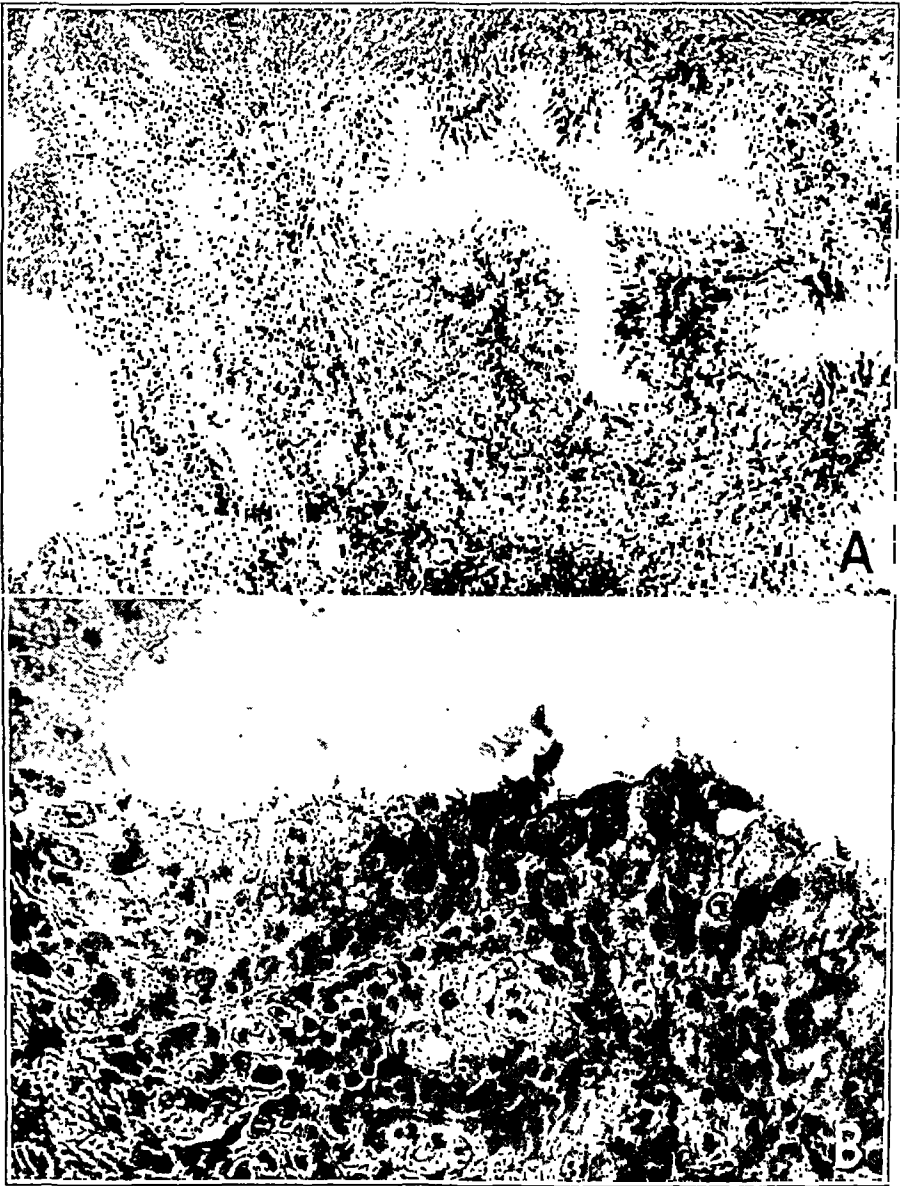


Fig. 9.—Bronchopneumonic bronchiectasis. *A*, transition from columnar to squamous epithelium over a portion of the bronchial wall and the granulation tissue, which comprises most of the bronchial wall; 2/3 power lens. *B*, a portion of the bronchus more highly magnified to show in detail the transition from columnar to squamous epithelium and the nature of the bronchial wall; 1/6 power lens.

19. Brock, R. C.: *Lancet* 2:1103. 1938.

when they are almost always found large and inflamed and obtrude themselves markedly when the fissure is being cleared."

Extensive collapse of the parenchyma was frequent in the excised lobes, though it was never really complete. These atelectatic lobes were

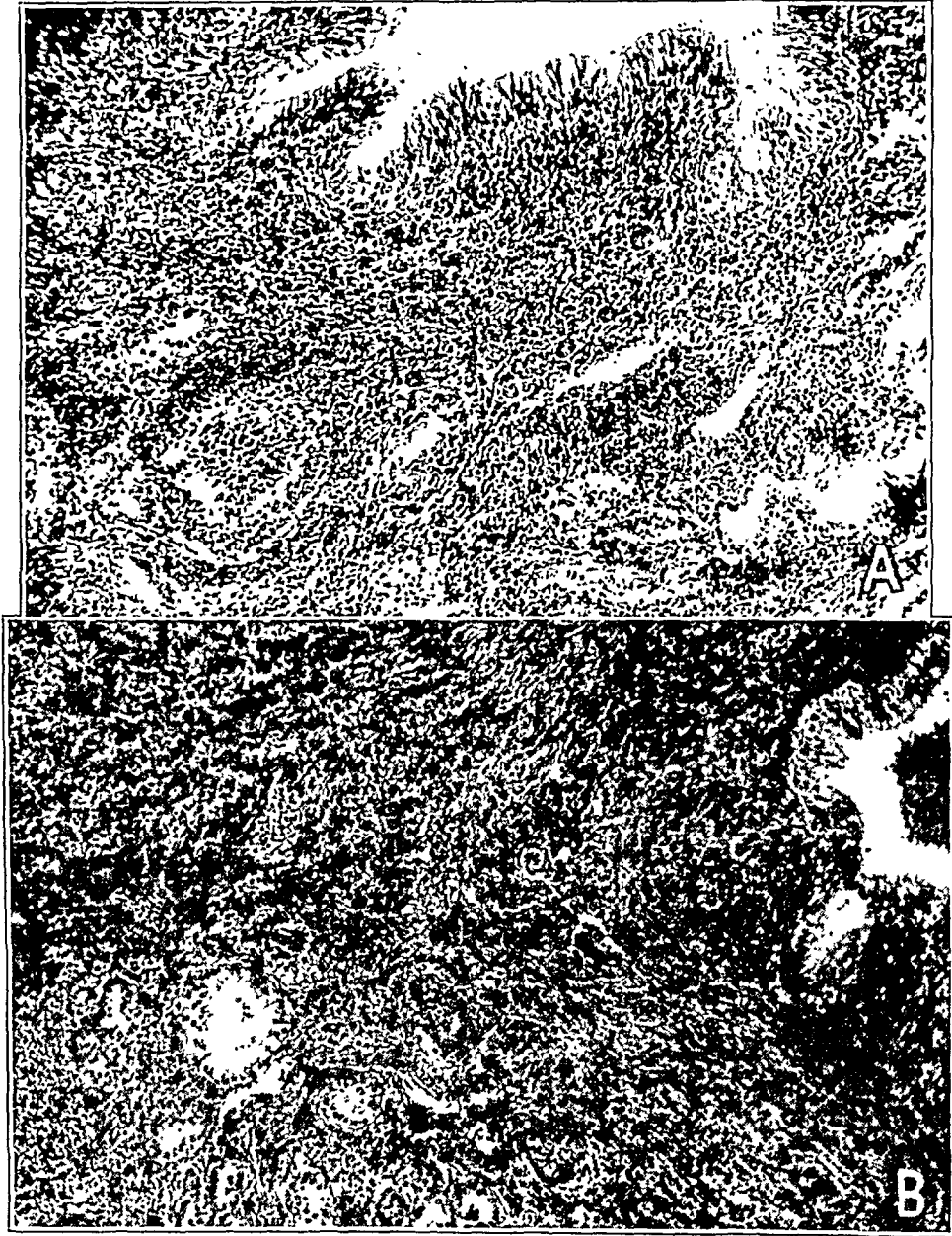


Fig. 10.—Bronchopneumonic bronchiectasis. *A*, the columnar epithelium which lines the bronchus has one break in its continuity; it is replaced by squamous epithelium. Vascular granulation tissue, in which there are a few "skeins" of scar tissue, is visible. No muscle tissue can be observed. $2/3$ power lens. *B*, a portion of the section in close proximity to the bronchus is magnified more highly to show an area of bronchopneumonic consolidation with destruction. $2/3$ power lens.

by no means free of inflammation and bronchial destruction, however—quite the contrary.

That these changes were the direct result of infective processes was indicated by the constant replacement of destroyed elements by granulation tissue, which showed definite evidence of organization into scar tissue in the usual way.



Fig. 11.—Bronchopneumonic bronchiectasis. *A*, damaged bronchus, in an emphysematous area, with debris in its lumen; $2/3$ power lens. *B*, a portion of the section more highly magnified to show the bronchial wall in detail; $1/6$ power lens. There is evidence of inflammation and the formation of scar tissue. No muscle is visible here, although a few strands were noted elsewhere in the wall of this bronchus.

The condition of the pleura must also be considered. The fact that gross pleural thickening was noted in 25 of 35 specimens suggests that pleural adhesions were a common feature of the excised lobes. As a

check on this, the records in 50 cases in which the patients were operated on by Mason have been studied. These cases were selected at random. It was found that in no less than 21 the diseased lobe was densely adherent, requiring the use of scissors for its removal. In only 7 cases was the pleura absolutely free.

These figures cannot, of course, be accepted as an indication of the incidence of pleural adhesions in cases of bronchiectasis in general, but they certainly show that adhesions are not uncommon.

These observations are directly at variance with those of Lander and Davidson, who reported that a normal bronchial wall, with negligible infection, and a free pleura were almost constantly found. The great frequency of collapse in bronchiectatic lobes in our series, a feature which they also stressed, was, however, in accordance with their experience.

Robinson's description of the bronchial wall agrees closely, however, with the appearance in this series of excised lobes, and Sauerbruch's account of granulations "springing up" in the diseased areas suggests that he observed similar changes.

Opie and associates,²⁰ Erb²¹ and McNeil, MacGregor and Alexander,²² whose studies are all comparatively recent, noted changes very like those recorded here, although rather more advanced. Excavation of the lung, for example, was a prominent feature in some of their cases, whereas it was only occasionally seen in the excised lobes in our series, and then in the bronchopneumonic group. They worked with post-mortem material, which is admittedly less satisfactory than "living" specimens, but their reports, being those of eminent pathologists, cannot be disregarded completely on this account. The photomicrographs published by Erb and by Opie and his associates are almost identical with those reproduced in this essay, as comparison will prove. MacCallum²³ also described pronounced bronchial damage.

The available evidence on the condition of the bronchial wall in bronchiectasis indicates, therefore, that the wall is frequently the subject of an infective process, which not uncommonly progresses to actual and possibly extensive, destruction. There is thus strong support for the view that definite weakening of the bronchi exists in many cases.

20. Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: *Epidemic Respiratory Disease*, St. Louis, C. V. Mosby Company, 1921.

21. Erb, I. H.: *Pathology of Bronchiectasis*, *Arch. Path.* **15**:357 (March) 1933.

22. McNeil, C.; MacGregor, A., and Alexander, A.: *Arch. Dis. Childhood* **4**:170, 1929.

23. MacCallum, W. G.: *Textbook of Pathology*, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 410.

In yet others there is every reason to suppose that the important function of the bronchi in the removal of the products of infection and foreign material, which was described in the foregoing section on the

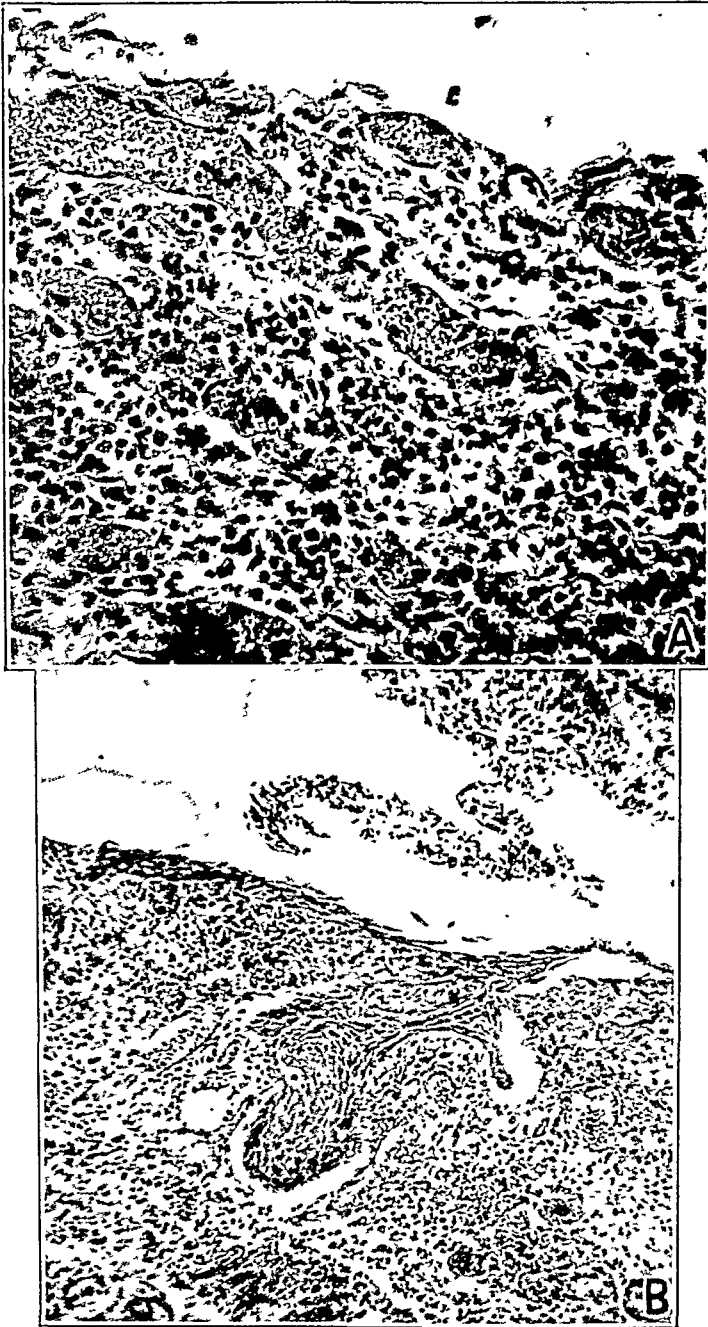


Fig. 12.—“*A*, wall of bronchus lined by granulation tissue (case 8; duration six and one-half weeks); $\times 240$. Note absence of muscle and elastic fibers. *B*, granulation tissue of bronchial wall becoming lined by squamous epithelium (same case); $\times 120$.”²¹

anatomy and physiology, is seriously interfered with, thus favoring persistence and extension of destructive processes.

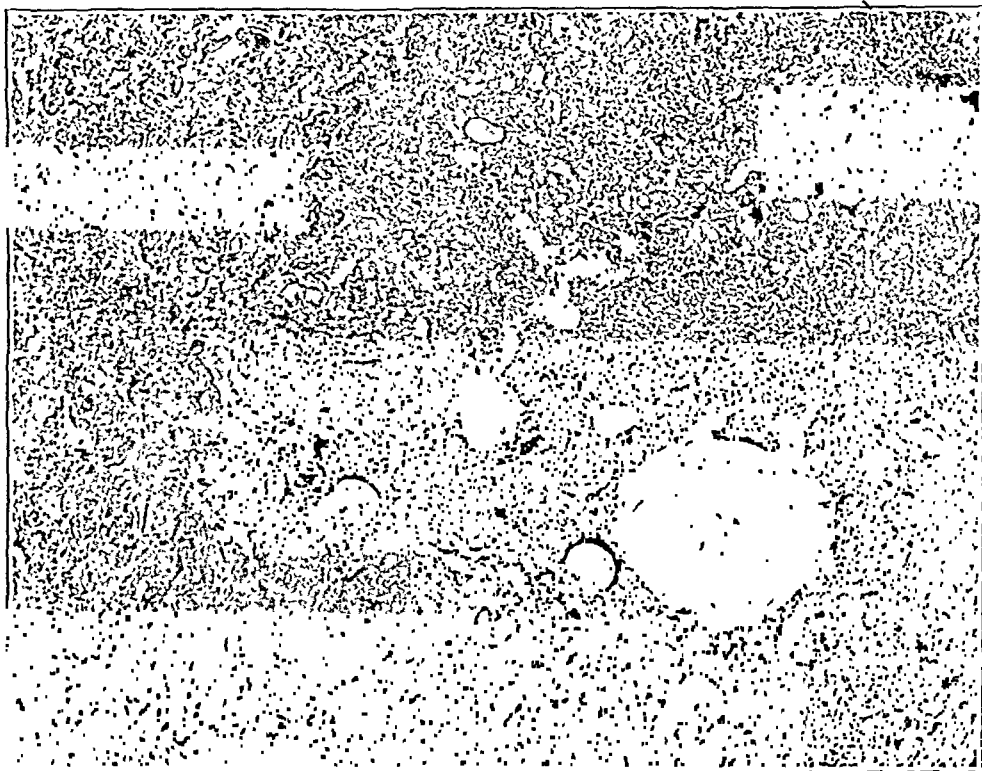


Fig. 13.—“Acute bronchiectasis with fissures extending through bronchial wall, which is marked by great engorgement of blood vessels: at one point a fissure has penetrated deep into the alveolar tissue and formed a small cavity containing purulent exudate and surrounded by fibrinous pneumonia.”²⁰



Fig. 14.—“Unresolved pneumonia with bronchiectasis, showing new formation of fibrous tissue about a greatly dilated bronchus, of which the epithelial lining has been lost.”²⁰

Strains and Stresses to Which the Wall of the Bronchi May Be Subjected.—The intrabronchial pressure was given by Hedblom²⁴ as 10 to 20 cm. of water. It is common knowledge that the normal bronchial wall, when supported by aerated lung tissue, withstands this pressure, although it is conceivable that a weakened bronchus might give way, as he suggested.

This pressure may be increased in several ways. Laennec²⁵ advanced the view, which has been repeated frequently, that the pressure of retained bronchial secretions might cause bronchial dilatation. However, this force cannot be measured, and the theory is not susceptible of proof or disproof. It remains as a possibility that a greatly weakened bronchus might yield to such pressure.

A much more certain, and probably more frequent, cause of raised intrabronchial pressure is collapse of the lung, which has been proved to act in this way. Airlessness of the neighboring parenchyma removes the strong "cushioned" support given normally to the bronchi by aerated lung tissue, thus producing a real intrabronchial pressure greatly above normal.

Lander and Davidson¹⁸ showed that the mean negative pleural pressure in cases of pulmonary collapse may rise to 27 cm. of water. This means that an atmospheric pressure of 37 to 47 cm. is acting on the bronchi, and these authors further showed that this pressure does dilate normal bronchi. They demonstrated bronchographically that immediate bronchial dilatation occurs when lobar collapse is induced in a healthy cat. Continuing their investigations, they studied cases of "black lobe." In certain cases of pulmonary tuberculosis in which treatment with artificial pneumothorax is being carried out, a sudden massive collapse of the partially collapsed lung sometimes occurs, producing the condition known from its appearance in the roentgenogram as "black lobe." Lander and Davidson demonstrated the presence of bronchial dilatation in such cases and its disappearance with an adequate refill of air. They repeated this procedure in ordinary cases of pulmonary collapse, with identical results. Furthermore, Ochsner,²⁶ Jennings²⁷ and Lander and Davidson reported cases of temporary atelectatic bronchiectasis. A definite atelectatic shadow, within which dilated bronchi were demonstrated, was studied by serial roentgenograms. Disappearance of the "collapse" shadow was accompanied by a return to normal of the bronchial caliber.

A case in my personal observation which bears on this point may be recorded here.

24. Hedblom, C. A.: Surg., Gynec. & Obst. **52**:406, 1931.

25. Laennec, R. T. H.: De l'auscultation médiate, Paris, J. A. Brosson & J. S. Chaudé, 1819, vol. 1, p. 124.

26. Ochsner, A.: Am. J. M. Sc. **179**:388, 1930.

27. Jennings, G. H.: Brit. M. J. **2**:963, 1937.

Mrs. G., a married woman of 34, was suddenly taken acutely ill, with breathlessness, high fever and pain in the left side of the chest. When seen ten days later, she was stated to be rather better. She was expectorating purulent sputum, but was still breathless on slight exertion. Examination of the chest revealed that the apex beat was in the left midaxillary line and that the left side of the chest was dull. Breathing was cavernous or tubular, and crackling rales were generalized over the left lung. The roentgenogram and bronchogram are reproduced. She was regarded as too ill to undergo a bronchoscopic examination at that time, and other measures directed toward securing reexpansion of the lung were employed. The abnormal signs did not disappear until three months later, when the last roentgenograms were taken.

Attention is directed to the opacity of the lung, with the presence of "cavities" in the early exposures, and the tortuosity and dilatation of the bronchi. In 1 instance iodized poppy seed oil entered the cavity, although it was prevented by obstructive secretions from entering the others. The later roentgenograms show restoration to normal.

This case appeared to be one of massive collapse of the lung associated with bronchial dilatation, which disappeared when the lung reexpanded.

It therefore becomes evident that the rise of intrabronchial pressure consequent on pulmonary collapse can produce dilatation of normal bronchi. How much more readily will such a force dilate bronchi weakened by disease?

Persistent coughing was advanced as a cause of increased intrabronchial pressure which might act as a dilating force, but the suggestion was refuted by Hedblom and by MacCallum,²³ who pointed out that pressure due to coughing is counteracted by the resistance of the diaphragm and of the chest wall.

Finally, extensive parenchymal scarring as a cause of bronchiectasis was ably advanced by Corrigan,²⁸ who expressed the belief that counteracting scar tissue might dilate the bronchi by traction. This view received recent support from Findlay and Graham,²⁹ but in general finds little credence at present. Pathologic evidence does not support it. Bronchiectasis can exist without significant scarring,³⁰ and extensive fibrosis is not infrequently seen without bronchiectasis, as in certain cases of tuberculous and nontuberculous pulmonary fibrosis.

In the present series the stellate appearance of the bronchial lumen, described by Opie, was regularly observed when bronchial destruction was pronounced. It could not, however, be attributed to contraction of parenchymal scar tissue, for it occurred when this was slight or absent. Furthermore, when scarring was present, the collagenous strands were peribronchial and did not run in bands from bronchus to bronchus or outward to unite with pleural scar tissue.

28. Corrigan, D. J.: *Dublin J. M. Sc.* **13**:266, 1838.

29. Findlay, L., and Graham, S.: *Arch. Dis. Childhood* **2**:71, 1927.

30. Robinson.¹⁵ Sauerbruch.¹⁷ Lander and Davidson.¹⁸

A more likely way in which pulmonary scarring might act is by weakening the support of the bronchi, through its replacement of the normal, functioning lung tissue, in much the same way as was just described in the discussion of atelectasis. MacCallum emphasized the possible dilatation produced by expiration against resistance, such as is likely to occur when a partial bronchial obstruction, due to stenosis of the bronchus or pressure from without, acts on a weakened bronchial

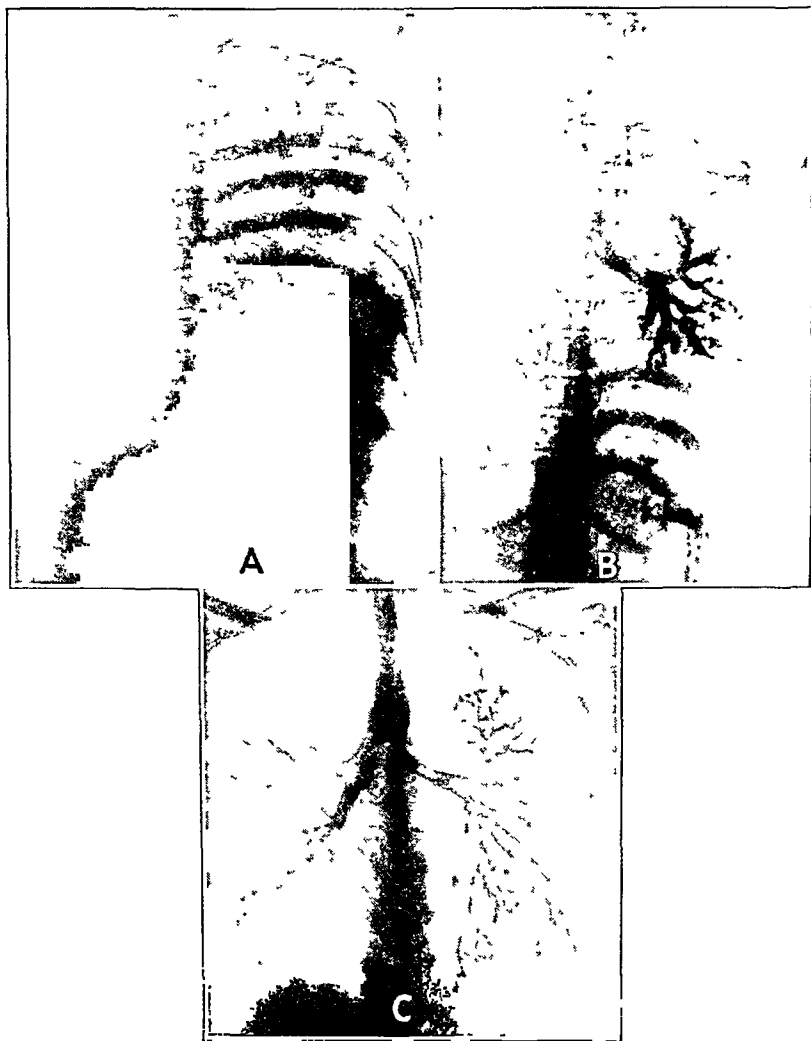


Fig. 15.—*A*, a roentgenogram of Mrs. G. made in May 1938. Note the general opacity of the pulmonary field and the numerous "cavities" within the field. The heart and trachea are displaced to the left. *B*, a bronchogram of Mrs. G. made in May 1938. Note the tortuosity and irregular dilatation of the bronchi. No iodized poppyseed oil has entered the "cavities" or the finer bronchi, which are evidently obstructed. *C*, a second bronchogram of Mrs. G. made in August 1938. The appearance of the bronchial tree is normal. The heart and trachea have returned to a normal position, and the opacity and "cavitation" have disappeared from the left pulmonary field.

wall. This possibility again is theoretic and has neither been proved nor disproved. It is undoubtedly possible that such dilatation does occur, but it is unlikely that it is at all frequent. As will be seen in the following section on etiology, bronchial obstruction is a frequent predisposing factor in bronchiectasis, but seems to act more often by favoring collapse or by hindering the removal of infection.

Comment: It appears from the foregoing evidence and general argument that weakening of the bronchial wall is frequent in bronchiectasis and that various strains and stresses may act on it as a dilating force, under abnormal conditions, whether it is weakened or no. The chief of these, and the only one the action of which has as yet been proved, is pulmonary collapse.

How is bronchial dilatation actually produced?

It has become obvious that no arbitrary answer can be accepted.

A damaged, and therefore weakened, bronchial wall is potentially liable to dilatation, but such dilatation need not necessarily occur. Any significant increase in the normal intrabronchial pressure will, however, cause the bronchus to dilate. Such a dilating force may be any of those which have previously been mentioned, and bronchiectasis can thus be produced in various ways. Furthermore, normal bronchi will dilate when subjected to excessive strain and will remain dilated until this strain is removed.

One must, therefore, recognize the probable existence of cases of chronic bronchial infection in which dilatation has not occurred, but is liable to occur. In such cases the patient must be watched. Cases in the present series which support this view will be described in the section on the roentgenographic features. These are instances of apparent "spread" of bronchiectasis, such as were recorded by Roles and Todd.³¹

On the other hand, bronchial dilatation does not necessarily mean that the bronchi are diseased, and the differentiation of the cases in which disease is lacking is important if unnecessary operations are to be avoided. Lander and Davidson were insistent on this point. Although evidence has been adduced which minimizes the probable frequency of such cases, the obligation to recognize their existence remains.

The cause of bronchial dilatation in those cases in the present series in which the excised lobes were placed in the bronchopneumonic group must be referred to before closing this section. In those, it will be remembered, bronchial destruction was more advanced, as a rule, and in none was damage slight. They were all cases in which parenchymatous changes were prominent, and the view is taken that the seriously weakened bronchi were in this way partially deprived of their main resistance to dilatation, namely, the normal aeration of the peribronchial alveoli.

31. Roles, F. C., and Todd, G. S.: *Brit. M. J.* **2**:639, 1933.

Other forces, such as the weight of retained secretions, the obstruction to expiration which these would cause (of MacCallum) and localized areas of collapse, may also have played a part. Furthermore, in a few cases areas of actual excavation of the lung were seen. The bronchial wall was completely deficient in one place, the margin of the lumen being formed only by lung tissue at this point. This condition resulted from a cavitation process rather than from true dilatation, perhaps, but is worthy of mention.

CONGENITAL BRONCHIECTASIS

There is a well defined and widely recognized congenital bronchial anomaly which is generally known as "congenital cystic disease of the lung." Two cases in the present series were regarded as instances of this abnormality, although the diagnosis was not asserted with certainty, owing to the absence of an autopsy in either case. It is no doubt true, as Warner³² and Kartagener³³ showed, that cases are, from time to time, erroneously regarded as examples of congenital cystic disease, but this fact does not affect the established existence of the condition. Many cases are now on record in which the true nature of the disease was verified by actual examination of the affected organs. The reports of Koontz,³⁴ Schenck,³⁵ Fleming,³⁶ Croswell and King,³⁷ Hennell³⁸ and others are conclusive.

The mode of origin is still in dispute, but the general view seems to support the theory that the abnormality is a failure of canalization of the smaller or terminal bronchioles, with arrested development of the corresponding area of lung, which becomes cystic. These cysts may be single or multiple and at birth are filled with a milky, opalescent fluid similar to or identical with the contents of the fetal bronchial system. Later this fluid may be expelled and the cysts remain as air cysts or become infected. A case in which infection occurs may be difficult or impossible to distinguish clinically and even pathologically³² from acquired bronchiectasis, but the cases in which infection is lacking do not suggest bronchiectasis.

It is indeed debatable whether this anomaly should be classed as bronchiectasis at all. No less an authority than Sauerbruch,³⁹ however, has advanced the view that a considerable number of cases in which there

32. Warner, W. P.: *Quart. J. Med.* **3**:401, 1934.

33. Kartagener, M.: *Beitr. z. Klin. d. Tuberk.* **85**:45, 1934.

34. Koontz, A. R.: *Bull. Johns Hopkins Hosp.* **37**:340, 1925.

35. Schenck, S. G.: (a) *Am. J. Roentgenol.* **35**:604, 1936; (b) *Diagnosis of Congenital Cystic Disease of the Lung*, *Arch. Int. Med.* **60**:1 (July) 1937.

36. Fleming, G. B.: *Arch. Dis. Childhood* **9**:201, 1934.

37. Croswell, C. U., and King, J. C.: *Congenital Air Cyst of Lung: Report of Case*, *J. A. M. A.* **101**:832 (Sept. 9) 1933.

38. Hennell, H.: *Cystic Disease of Lung*, *Arch. Int. Med.* **57**:1 (Jan.) 1936.

39. Sauerbruch, F.: *Arch. f. klin. Chir.* **180**:312, 1934; footnote 17.

is all the appearance of bronchial dilatation without the presence of cysts are in reality instances of congenital bronchial deformity. In such cases the bronchi would, of course, be liable to secondary infection, although he did not stress this point. When the difficulty of differentiating congenital cystic disease in the presence of infection is admitted, the difficulty which is likely to arise in the recognition of Sauerbruch's "congenital type" may be imagined.

Sauerbruch described a series of 50 cases in which infection was apparently insignificant. Lotzin, who with Sauerbruch examined the lobes excised in these cases, reported that histologic appearance as follows:

The bronchial epithelium was ciliated and consisted of several layers. The muscle was irregular and was hypertrophied, while only irregular strings of elastica were seen. The bronchi were described as "ending blindly," without alveolar connections. Mucous glands were abnormally numerous, and cartilage was poorly developed. There was "no sign of inflammation, past or present."

In all these cases the patients were children and the disease in each case was confined to one lobe, nearly always the lower lobe of the left lung. Sauerbruch expressed the belief that this is the rule in cases of this type, but when one compares his series with 381 cases of congenital cystic disease collected by Schenck, confidence is shaken. In Schenck's cases the disease was right sided in 157 and left sided in only 136, while it was bilateral in 78.

Sauerbruch¹⁷ explained the left-sided unilobar incidence in his cases embryologically. In the fifth week of fetal life⁴⁰ the thoracic cavity enlarges and the ducts of Cuvier, running in the septum transversum, elongate and enter the sinus venosus at a much more acute angle. At this period the lung buds are growing rapidly, and Sauerbruch expressed the belief that in certain cases the left duct in particular presses on the embryonic lung, interfering with the development of that portion which forms the lower lobe. This appears to be a reasonable hypothesis, once the congenital origin of lobar bronchiectasis is established.

No other author, however, as far as was discovered, confirmed the histologic observations of Sauerbruch and Lotzin. The evidence in the literature which has been cited emphasized the changes produced by infection, with the exception of that of Lander and Davidson, who nevertheless discovered no indication of congenital bronchial defect. The material examined in the present study also failed to reveal similar changes.

This statement is, of course, quite another thing from a denial of the existence of Sauerbruch's "congenital type," and no such denial is contemplated. The negative evidence suggests that the frequency of its

40. Keith, A.: *Human Embryology and Morphology*, ed. 4, London, E. Arnold, 1921, p. 346.

occurrence is less than Sauerbruch stated, but, in fact, the root of the matter is that the existence of congenital defects in a seriously damaged bronchus is as difficult to disprove as to prove.

Evidence of associated congenital defects is to be found in the literature. Kartagener³³ reported cases of congenital heart disease and situs inversus in association with bronchiectasis and met with instances of familial bronchiectasis. There is a possibility that the bronchiectasis in these cases was secondary to the abnormal cardiac condition. Congenital heart disease is recognized as a cause of pulmonary collapse, and I saw several cases in which this relation existed.

A report of congenital abnormalities of the nasal sinuses in cases of bronchiectasis was also suggestive, although it must be admitted that such evidence is mainly circumstantial.

A large literature has grown up around the subject of congenital bronchial defect, and although the great majority of the articles deal with congenital cysts of the lung, whether single or multiple, no solution has been found for the problem under discussion. It is believed that a fair presentation of the position has been made, and further discussion is considered unnecessary. Neither the occurrence or frequency of congenital bronchiectasis nor its true relation to congenital cystic disease of the lung can be established on the evidence at present available. Evidence which seems opposed to the existence of a "congenital type" is also of suggestive value only, and the matter must, perforce, be left open.

ETIOLOGY

Etiology and pathogenesis have usually been discussed together in the literature on bronchiectasis, and it is felt that this may have contributed to a certain confusion as to the causation of this condition.

Therefore it seemed desirable in this essay first of all to establish as well as possible the mode or modes of pathogenesis and then to discuss the etiology in the light of this.

With regard to indirect etiologic factors, no particular sex incidence could be determined, but the question of age was found to be important. The age of onset was not as a rule dealt with statistically, as writers concentrated rather on the age at which their patients were first seen. Farrell,⁴¹ however, stated that 80 per cent of his patients dated their symptoms from the first decade of life, and my experience with the present series is even more emphatic as regards the early onset of symptoms.

In 45 of my 68 cases, or 66 per cent, symptoms dated from the first five years of life, and in 37 of the 45, from the first two years. In only

41. Farrell, J. T., Jr.: Importance of Early Diagnosis in Bronchiectasis: Clinical and Roentgenologic Study of One Hundred Cases, *J. A. M. A.* **106**:92 (Jan. 11) 1936.

23 cases, or 34 per cent, was there a history of later onset, and even in a number of these symptoms dated from late childhood. It is, of course, impossible to say whether bronchial dilatation was present throughout the intervening period, but it is at least obvious that the processes which produced it were in operation. It must be emphasized that symptoms of one sort or another were constantly present in all cases.

Bronchiectasis, in its origin, is therefore to an important extent a disease of childhood, quite apart from "congenital predisposition." The infinitely better results attending active medical treatment and operation in childhood increase the significance of this fact, since if in two thirds of all cases the condition has its origin in childhood, early recognition should greatly improve prospects for the treatment of the disease as a whole.

Bronchiectasis is a disease of those parts of the world in which infections of the respiratory tract are particularly common. Nothing further need be said as to the indirect etiologic factors.

The direct etiologic factors can readily be assessed from the foregoing account of the pathogenesis. They may be conveniently divided into the following groups:

Causes of bronchial damage:

1. Infections of the bronchopulmonary system and other direct causes.
2. Any conditions which predispose to the occurrence or recurrence of such infections.
3. Factors favoring the persistence or extension of bronchial infection.

Causes of abnormal bronchial strain:

1. All causes of lobar or pulmonary collapse and all conditions predisposing thereto.
2. Causes of parenchymal damage or destruction.
3. Factors favoring the retention of large amounts of weighty secretions within the bronchi.

CAUSES OF BRONCHIAL DAMAGE

Infections.—Almost any infection of the respiratory tract, of which the most obvious example is bronchopneumonia, can be included under this heading. It is important to recognize, however, that the original infection may be comparatively slight in its general effects, a fact accounting for the apparently "spontaneous" origin of symptoms, observed in 29 cases (43 per cent) of my series. As will be demon-

strated in the section on clinical features, this figure agrees well with that for most of the reported series.

The bacteriologic studies on bronchiectasis are not helpful, and a review of the literature forces one to the conclusion that any organism which is known to produce lesions in the respiratory tract may be concerned. Leys⁴² stressed the importance of Pfeiffer's bacillus, and Blake and Cecil⁴³ and Opie and his associates⁴⁴ also accused this germ, the former on experimental grounds. Smith⁴⁵ and Pilot and Davis,⁴⁶ on the other hand, claimed both on clinical and on experimental grounds that Vincent's spirochete is a frequent cause of bronchial damage leading to bronchiectasis. An extensive study by Greey⁴⁷ seemed to prove conclusively, however, that the great variety of organisms which may be found precludes any idea of a specific or predominating bacterial cause.

Extensive bacteriologic studies were not carried out in the present series, owing to Greey's conclusions. Tubercle bacilli were, however, consistently sought, with uniformly negative results.

Caution must always be observed in accepting without reserve the patient's statement of a history of a previous thoracic disease, as the diagnosis cannot be verified. However, the surveys of etiologic factors in the literature and in the present series were necessarily based on such histories and must be accepted for what they are worth. The results of these surveys were difficult to compare, because each author seemed to adopt a different grouping, but the constancy of a particularly high incidence of previous disease of the respiratory tract with a definite chronologic relation to the onset of symptoms was extremely suggestive.⁴⁸ This incidence was over 50 per cent, and the diseases most frequently mentioned were pneumonia, bronchopneumonia, bronchitis and influenza. Measles and whooping cough came low on the list. A comparison with the incidence in the present series may be of interest.

42. Leys, D.: *Chronic Pulmonary Catarrh*, London, H. K. Lewis & Co., Ltd., 1927.

43. Blake, F. G., and Cecil, R. L.: *J. Exper. Med.* **32**:691, 1920.

44. Opie, E. L.; Freeman, A. W.; Blake, F. G.; Small, J. C., and Rivers, T. M.: *Pneumonia Following Influenza*, *J. A. M. A.* **72**:556 (Feb. 22) 1919.

45. Smith, D. T.: *Am. Rev. Tuberc.* **15**:352, 1927; *Etiology of Primary Bronchiectasis*, *Arch. Surg.* **21**:1173 (Dec., pt. 1) 1930; *J. Infect. Dis.* **46**:303, 1930.

46. Pilot, I., and Davis, D. J.: *Studies in Fusiform Bacilli and Spirochetes: Their Rôle in Pulmonary Abscess, Gangrene and Bronchiectasis*, *Arch. Int. Med.* **34**:313 (Sept.) 1924.

47. Greey, P. H.: *J. Infect. Dis.* **1**:302, 1932.

48. (a) Fletcher, E.: *J. Thoracic Surg.* **4**:460, 1935. (b) Thorpe, E. S.: *Am. J. M. Sc.* **177**:759, 1929. (c) Hedblom.²⁴ (d) Farrell.⁴¹ (e) Ballou, Singer and Graham.¹³ (f) Findlay and Graham.²⁹

	Cases		Cases
Bronchopneumonia	22	{ Primary	19
		{ Measles	2
Lobar pneumonia	1	{ Whooping cough	1
		{ Primary	7
Bronchitis	14	{ Whooping cough	4
		{ Influenza	2
		{ Rubella (?)	1
Insidious, or "spontaneous" onset.....	29		

Influenza was less important and measles and whooping cough rather more important than in other series. The predominant position of bronchopneumonia was fully supported, however.

Murphy⁴⁹ and others reported an area of bronchiectasis at the site of a primary tuberculous lesion, and Eliasberg and Neuland⁵⁰ noted bronchiectasis in cases of epituberculosis.

Pulmonary abscess was often mentioned as a cause of bronchiectasis. This condition is really covered by what has already been said, as it is an infection of the respiratory tract. But Ballou, Singer and Graham¹³ stated that "chronic abscess" is always followed by bronchiectasis, and Warner reported that in 12 per cent of his cases the bronchiectasis was due to "lung abscess."¹¹ Without further examination, one would expect this condition to be a causative factor, since pulmonary destruction occurs. No case has actually been met with personally, but perhaps this was because patients who did not recover under medical treatment were operated on and their cases might not, therefore, come under the heading of "chronic" abscess. (Maxwell,⁵¹ however, in a large series of 315 cases found only 5 cases of bronchiectasis.) The evidence is thus conflicting, but it would appear that pulmonary abscess must be regarded as at least an occasional cause of bronchiectasis.

The recently imported condition of "pneumonitis" must also be mentioned, because a suppurative variety was recently described by Garland and Berridge⁵² as resulting in bronchiectasis in 2 out of 16 cases. The true existence of "pneumonitis" cannot be freely admitted in the absence of a pathologic basis, but reference to it cannot be omitted in view of numerous recent reports. I offer it as a possibility that these cases of "pneumonitis" may be instances of acute or suppurative bronchiolitis associated with instances of lobular collapse. The diagnosis, at present, appears to rest on the appearance of the roentgenograms.

Norris and Landis⁵³ insisted on the importance of inorganic dust as a cause of bronchial damage leading to bronchiectasis. They found

49. Murphy, J. E.: *Am. J. Roentgenol.* **31**:301, 1934.

50. Eliasberg, H., and Neuland, W.: *Jahrb. f. Kinderh.* **93**:88, 1920.

51. Maxwell, J.: *Quart. J. Med.* **3**:467, 1934.

52. Garland, A., and Berridge, F. R.: *Lancet* **1**:375, 1939.

53. Norris, G. W., and Landis, H. R. M.: *Diseases of the Chest*, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

that of 21 potters examined by them 10 showed bronchiectasis. This number is greater than I have had the opportunity of studying, as silicosis is rather uncommon in the north of England. In 2 cases of silicosis, however, the bronchi were normal. War gases were described by Farrell⁴¹ and Fletcher^{48a} as an occasional cause of bronchiectasis; here, again, I am unable to confirm this observation, owing to an insufficient number of cases. In 5 cases of chronic disability following gassing in the World War, however, the patients all showed normal bronchi. No cases of bronchiectasis due to inorganic causes were met with, therefore, but no intensive search for such cases has as yet been attempted.

Predisposing Factors.—Certain of the specific infectious fevers, particularly influenza, measles and whooping cough, are widely recognized as predisposing to the development of bronchopneumonia, although this association was noted in only 3 cases in the present series. Pink disease also appears to predispose to infection of the respiratory tract and bronchiectasis on occasion.⁵⁴

As a direct cause of the occurrence and recurrence of infection of the respiratory tract, great importance is attached in the literature to chronic sinusitis. A large number of articles have been devoted to the relation between chronic sinusitis and bronchiectasis, only a few of which can be referred to here. The generally accepted theory of sinusitis as a cause of bronchiectasis is that of the repeated direct aspiration of infective products from the nasal passages. This provides a continual reenforcement of an existing infection, even if it is not actually the origin of the primary infection itself.

Quinn and Meyer⁵⁵ introduced iodized poppyseed oil into the nasal passages during sleep. Subsequent roentgenographic examination showed iodized oil in the lungs in 5 of 11 persons. These authors also found sinusitis in 22 out of 38 cases of bronchiectasis.

Mullin⁵⁶ expressed preference for the theory of spread of infection through the lymphatics from the antrum to the main lymph ducts, and so by the great veins to the lungs. This idea has not gained general acceptance, and the theory of aspiration seems to be the most likely one.

Graham⁵⁷ and Thomson⁵⁸ both noted the association of sinusal infection with bronchorrhea. Graham made numerous observations on bronchial fistulas and noted that there was an immediate inflammatory

54. Spence, J. C.: Personal communication to the author.

55. Quinn, L. H., and Meyer, O. O.: Relationship of Sinusitis and Bronchiectasis, *Arch. Otolaryng.* **10**:152 (Aug.) 1929.

56. Mullin, W. V.: *Ann. Otol., Rhin. & Laryng.* **30**:685, 1921.

57. Graham, E. A.: Surgical Treatment of Pulmonary Suppuration in Children, *J. A. M. A.* **87**:806 (Sept. 11) 1926.

58. Thomson, St. C.: *Practitioner* **92**:745, 1914.

reaction at the fistula when any exacerbation of the sinusal infection occurred. Rist⁵⁹ found an association of sinusal infection with cough.

Sergent⁶⁰ was the first to draw attention to the clinical connection between infections of the upper and those of the lower respiratory tract, and a great deal has been written on this subject since his article, published in 1916.

Webb and Gilbert,⁶¹ in a roentgenographic study of all the sinuses in cases of disease of the chest, found that in only a few cases of bronchiectasis was there no evidence of chronic infection of the accessory sinuses. Bilateral empyema of the antrums was the lesion most frequently encountered. Other communications were made by Dennis,⁶² Davis,⁶³ Young,⁶⁴ Moll,⁶⁵ Ballou, Singer and Graham¹³ and others. The most recent series, and the largest, was that of Walsh and Meyer.⁶⁶ Of 217 cases of bronchiectasis, there was associated sinusitis in 45, or 66.8 per cent. No relation between the severity of the sinusitis and the extent and duration of the bronchiectasis could, however, be established. Symptoms referable to the sinusitis were unusual. The sinuses were especially and fully examined in each case in an active search for infection, and a diagnosis of sinusitis was made only when gross pus was demonstrable in one or more of the sinuses.

On the pathologic side, reference may be made to papers by Opie⁶⁷ and by Ebbs.⁶⁸ In a review, Opie recorded that sinusal infection is almost always found in patients with influenzal pneumonia and that influenza may be a prebronchiectatic condition. Ebbs found evidence of sinusitis or otitis at autopsy in 86 per cent of 200 cases of pneumonia.

What conclusion is one to draw from this mass of evidence? It would seem reasonably clear from the aforementioned reports that infective material can and does reach the bronchi from the nasal sinuses and often gives origin to or exacerbates bronchial infection. It also appears probable that in patients who are expectorating large amounts of purulent sputum daily the reverse process is likely to occur. The literature offers no evidence which enables one to differentiate between these two possibilities, and it seems reasonable that infection occurs in

59. Rist, E.: *Rev. de la tuberc.* **7**:705, 1926.

60. Sergent, E.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **40**:1424, 1916.

61. Webb, E. B., and Gilbert, G. B.: *Bronchiectasis and Bronchitis Associated with Accessory Sinus Disease*, *J. A. M. A.* **76**:714 (March 12) 1921.

62. Dennis, F. L.: *Ann. Otol., Rhin. & Laryng.* **33**:451, 1924.

63. Davis, E. D. D.: *J. Laryng. & Otol.* **43**:495, 1928.

64. Young, R. A.: *J. Laryng. & Otol.* **43**:470, 1928.

65. Moll, H. H.: *Quart. J. Med.* **1**:457, 1932.

66. Walsh, T. W., and Meyer, O. O.: *Coexistence of Bronchiectasis and Sinusitis*, *Arch. Int. Med.* **61**:890 (June) 1938.

67. Opie, E. L.: *The Pathologic Anatomy of Influenza*, *Arch. Path.* **5**:285 (Feb.) 1928.

68. Ebbs, J. H.: *Proc. Roy. Soc. Med.* **30**:1407, 1937.

both directions. Data from the present series do not suggest any solution of the problem because of the inadequate number of cases in which the patient was subjected to full investigation, including proof puncture. In only 13 of the 68 cases could sinusitis be proved, and in all these it was antral. It is suggested here that the sinusitis is in many cases secondary, but that once established it may cause repeated reinfection of the bronchi, setting up a vicious circle. The observed fact that the vast majority of sinusal infections associated with bronchiectasis are antral supports this view.

Unfortunately, no authors were able to point to any improvement in the condition in the chest after treatment of the nasal infection, and this experience is corroborated by the few cases in the present series. It would appear that the most reasonable attitude for the future is to search for sinusal infection in all cases of bronchiectasis in which operation is to be performed and to deal adequately with such infection after operation, in order to prevent further damage. This practice is now being carried out, I understand, in the department of thoracic surgery at the Newcastle General Hospital.

Chronic tonsillitis was not found by other authors to have any particular association with bronchiectasis, and none was noted in the present series.

Factors Favoring the Persistence or Extension of Bronchial Infection.—The chief of these factors is bronchial obstruction. If a bronchus is obstructed, drainage is hindered, and the tubes distal to the obstruction cannot adequately rid themselves of infective products. These, if retained, continue and may extend the process of bronchial damage.

Eloesser,⁶⁹ in a detailed study of bronchial obstruction, emphasized its importance in the production of bronchiectasis and classified its causes under three heads: intramural, mural and extramural. With regard to the intramural causes, the effects of foreign bodies within the bronchi are well known and need only be mentioned. There was only 1 illustration of this in the present series, the case of a boy who inhaled a portion of a walnut into his trachea. An attempt at removal of the nut, which was balanced at the carina, resulted in a portion entering the left bronchus. Bronchiectasis of the lower lobe of the left lung resulted.

Of recent years, particular attention has been directed to the obstructive effect of viscid bronchial secretions, due in most cases, though perhaps not in all, to bronchial infection. Chevalier Jackson⁷⁰ demonstrated this phenomenon repeatedly by aspirating viscid mucopurulent material from the bronchi in cases of postoperative atelectasis, with resultant reexpansion of the collapsed lung or lobe.

69. Eloesser, L.: J. Thoracic Surg. 1:485, 1932.

70. Jackson, C.: (a) Proc. Roy. Soc. Med. 24:1, 1930; (b) footnote 6.

The presence of a bronchial adenoma may also cause gross bronchial obstruction with collapse of the lung and resultant bronchiectasis. I met with 1 example of this, in a patient whose case was not included in the present series. No lobectomy has been performed on the patient, who suffered from a suppurative bronchial infection which subsided after removal of the adenoma.

Mural obstruction consists mainly of bronchial stricture, which may be inflammatory or neoplastic. Inflammatory stricture may result from local trauma and secondary infection, theoretically, or from tuberculous or syphilitic ulceration. Tuberculous bronchial stenosis was reported by Eloesser,⁷¹ Cohen and Higgins,⁷² Phelps,⁷³ Bucher⁷⁴ and others. Cohen and Higgins reported 19 cases, in 13 of which bronchiectasis was proved and in 4 of which symptoms were present, though bronchiectasis was not demonstrated. Bucher described a case of inflammatory bronchial obstruction due to tuberculosis, and Andrews⁷⁵ observed similar cases. Lightwood and Wilson⁷⁶ demonstrated a case of bronchiectasis associated with bronchial stenosis in a boy of 5 who had a strongly positive tuberculin reaction. Recently Morlock and Hudson⁷⁷ published a brief but interesting account of their experiences with bronchoscopy in cases of pulmonary tuberculosis. They found that obstructive lesions were not infrequent and divided the cases in which there was obstruction into four groups:

1. Those in which the obstruction appears to be due to an enlarged gland, or tuberculoma. [This group is discussed later.]
2. Those in which gelatinous tuberculous granulations obstruct the bronchus.
3. Those in which pulmonary fibrosis with resulting deformity of the bronchus cause the block.
4. Those in which the bronchial mucous membrane is so edematous as to cause narrowing of the lumen, which is filled with tenacious secretion.

Syphilitic bronchial stenosis was studied by Conner,⁷⁸ who found 15 examples of bronchiectasis in 128 collected case reports. The presence of this condition in all of these cases was proved bronchoscopically, except in Conner's own cases, in which it was verified at autopsy.

In the present series, no examples of tuberculous stenosis were found, although it is true that in several of the cases there was no bronchoscopic examination. A positive Wassermann reaction was reported in 3 cases, but no evidence of stricture was found, although in

71. Eloesser, L.: *Am. Rev. Tuberc.* **30**:123, 1934.

72. Cohen, S. S., and Higgins, G. K.: *Am. Rev. Tuberc.* **36**:711, 1937.

73. Phelps, K.: *Ann. Otol., Rhin. & Laryng.* **45**:1133, 1936.

74. Bucher, C. J.: *Pulmonary Tuberculosis Associated with Acute Bronchial Obstruction*, *J. A. M. A.* **90**:1289 (April 21) 1928.

75. Andrews, C. H.: *Canad. M. A. J.* **33**:36, 1935.

76. Lightwood, R., and Wilson, R.: *Arch. Dis. Childhood* **11**:321, 1936.

77. Morlock, H. V., and Hudson, E. H.: *Brit. M. J.* **1**:381, 1939.

78. Conner, L. A.: *Am. J. M. Sc.* **126**:57, 1903.

1 case a syphilitic ulcer of the vocal cords was present. In all 3 cases a bronchoscopic examination was made.

Adams and Escudero⁷⁹ claimed to have proved that bronchiectasis occurs only if the obstruction is incomplete, and it seems reasonable to suppose that aerobic infection is unlikely to progress if the obstruction is complete. These authors worked with dogs and did not find bronchiectasis with atelectasis resulting from complete obstruction. This information cannot be accepted as applying to human beings. In any event, the observations at autopsy were not conclusive. It is known that dilatation is only temporary in cases of bronchial obstruction, unless bronchial destruction has occurred.

As regards the present problem, Adams and Escudero seem to have shown that infection does not persist when obstruction is complete. They produced bronchial stricture in dogs by means of either thermal cauterization or a solution of silver nitrate and then introduced cultures from an abscess of a human lung. Bronchiectasis occurred in all 15 dogs within six weeks, except in 1 which died of distemper on the third day. They next introduced the culture suspended in iodized poppyseed oil and found no bronchial damage in five weeks. The choice of iodized oil seems rather unfortunate, owing to its known antiseptic properties, but the evidence is strongly suggestive. Clinically, however, it is probable that obstruction is rarely absolute for more than a short time, as, even with a foreign body, secretions can be expelled by coughing. It is more likely that obstruction is either partial or valvular, allowing a little air to enter, while preventing its exit during quiet expiration. This air may be insufficient to reinflate a collapsed lobe, although perhaps increasing bronchial pressure slightly. But it will yet be adequate, in all probability, to nourish the intrabronchial infection.

Extramural obstruction is caused typically by pressure of an aortic aneurysm or a mass of malignant glands, as is well recognized. An interesting and less widely appreciated cause of extramural obstruction is pressure by tracheobronchial or bronchopulmonary lymph nodes which have enlarged because of tuberculous infection. Vinson⁸⁰ described bronchiectasis due to this type of extramural obstruction, and de Bruin⁸¹ noted atelectasis, but did not mention bronchiectasis. A bitonal cough and the expiratory stridor which accompany such obstruction were described by Wallgren,⁸² in a classic article on infantile primary tuberculosis.

One example of bronchiectasis due to extramural obstruction occurred in the present series. This was the case of a man of 27 who

79. Adams, W. E., and Escudero, L.: *Tubercle* 8:351, 1938.

80. Vinson, P. P.: *M. Clin. North America* 19:453, 1935.

81. de Bruin, M.: *Arch. Dis. Childhood* 11:65, 1936.

82. Wallgren, A.: *Primary Pulmonary Tuberculosis in Childhood*, *Am. J. Dis. Child.* 49:1105 (May) 1935.

complained of persistent cough and purulent expectoration, of four years' duration. He had had pleurisy five years before and a "feverish cold" four years before and dated his symptoms from the latter. He was found to have bronchiectasis of the middle lobe of the right lung, and died within twenty-four hours of an operation on his chest. At autopsy, evidence of healing tuberculosis was noted in the upper lobe of the right lung, and the bronchopulmonary and hilar glands were greatly enlarged. These glands appeared to be pressing on the bronchus leading to the middle lobe of the right lung, so that the lumen was greatly narrowed.

Tuberculosis is thus far from being an unimportant factor in the causation of bronchiectasis, and Potter⁸³ expressed the opinion that the incidence of "bronchiectasis associated with chronic fibro-ulcerative lesions is high." It is chiefly as a cause of bronchial obstruction that tuberculosis appears to act, although Murphy's⁴⁹ report of bronchiectasis at the site of a primary tuberculous lesion and Eliasberg and Neuland's observation of bronchiectasis in epituberculosis have already been cited.

From the foregoing discussion it appears that bronchial obstruction is an important cause of bronchiectasis, but that incomplete obstruction is a more potent factor than is complete obstruction in the propagation of infective bronchial damage. One further possible cause of the persistence of a bronchial infection must be referred to. As has been mentioned before, it seems probable that superficial but extensive bronchial infection may paralyze or hinder the normal bronchial function of the expulsion of foreign material, and so favor the retention of infective products, with consequent persistence and extension of bronchial infection. This probability cannot be proved, but the experiments of Hudson and Jarre,⁸ which were cited in the section on anatomy and physiology, offer indirect evidence. The probability is mentioned as a deduction from what is known of the normal bronchial function.

CAUSES OF ABNORMAL BRONCHIAL STRAIN

1. *All Causes of Lobar or Pulmonary Collapse and All Conditions Predisposing Thereto.*—The prime cause of collapse of the lung is bronchial obstruction, which must be of sufficient severity to prevent the entry of air. Lichtheim⁸⁴ demonstrated that the air within the part of the lung distal to the obstruction was then absorbed, allowing the lung to collapse.

All the causes of bronchial obstruction which were described in the preceding section are therefore likely to be causes of collapse, provided they fulfil this condition; that is, they must exclude air from the part of the lung distal to the obstruction. This is rather a matter of the

83. Potter, B. P.: *Am. J. Roentgenol.* **31**:308, 1934.

84. Lichtheim (quoted): *Arch. f. exper. Path. u. Pharmakol.* **10**:54, 1878.

degree of obstruction in any particular case than of the origin of the obstruction itself, although, of course, certain types of obstruction are more likely to be complete than others.

Several causes of obstruction must, however, be accorded special consideration. The first of these is obstruction by intrabronchial secretion, which was emphasized as a cause of postoperative collapse on experimental and clinical grounds by Band and Hall⁸⁵ and by Elliott and Dingley.⁸⁶ It is true that this condition was mentioned in the preceding section, but, owing to its special importance in the present connection, something further must be said. The history and usual clinical course have been described in a previous communication.⁸⁷ Briefly, the condition is one of bronchitis or bronchiolitis, in which the bronchi of a lobule, a lobe or a lung become acutely infected and inflamed, with consequent swelling of the mucosa and production of a viscid secretion, which together block the lumen. Collapse of the corresponding area of the lung distal to the obstruction occurs, and this collapse may be lobular, lobar or pulmonary, according to the grade and number of the obstructed bronchi or bronchioles. Such obstructions occur typically after abdominal operations, but there can be little doubt that they occur "spontaneously" much more frequently.

Any illness causing or associated with bronchitis can cause collapse, such as measles, whooping cough or influenza. Few cases in the present series were instances of atelectatic bronchiectasis following whooping cough. In the great majority of cases, recovery with complete reexpansion of the collapsed lung, takes place in a few days, usually after the expectoration of a varying amount of sticky, mucopurulent sputum.

For this reason, in few such cases do the patients attend a hospital, and in fewer still are they studied roentgenographically. The true condition is thus readily overlooked, and the illness is apt to be diagnosed as "abortive pneumonia."

In a proportion of cases, however, the failure of this early reexpansion to occur is due in all probability to a more persistent infection or to inefficient breathing from any cause or to both of these together.

From the studies of Lander and Davidson,¹⁸ it is known that bronchial dilatation is almost certain to be present as long as the collapsed state persists, and the after-history then depends on two factors: the dose and virulence of the infecting organisms and the duration of the collapse. The longer the lung remains collapsed, the more likely is bronchial dilatation to become permanent. The case reported in the section on pathogenesis shows that restoration to normal is possible even after several months and that reexpansion can be assisted by suitable

85. Band, D., and Hall, I. S.: *Brit. J. Surg.* **19**:387, 1932.

86. Elliott, T. R., and Dingley, L. A.: *Lancet* **1**:1305, 1914.

87. Ogilvie, A. G.: *Newcastle M. J.* **15**:30, 1935.

measures, but every effort should be made to recognize and deal with the condition at an early date, if permanent bronchiectasis is to be avoided. The high incidence of atelectatic bronchiectasis in the present series supports the view that "spontaneous" collapse of the lung is an important cause of bronchiectasis.

Traumatic collapse was studied by Bradford,⁸⁸ who emphasized the frequency of contralateral collapse, which suggests some reflex action. A reflex mechanism was proposed by Scott⁸⁹ as a cause of postoperative atelectasis. He stated that such a reflex, possibly vagal, may act in one or more of three ways: It may produce a change in vasomotor control which results in an excess of bronchial secretion; it may cause bronchial spasm, or it may lead to a swelling of the mucous membrane. However this may be, it is likely that traumatic collapse is rare as a cause of bronchiectasis because patients thus affected quickly recover completely or die. The rarity of collapse in cases of asthma is rather against this idea of Scott's, in any event.

Pleural inflammation and friction occur in cases of atelectasis, and caution must be observed in attributing the collapse to this cause.

Pleural effusions and pneumothorax, whether spontaneous or artificial, collapse the lung in a different way and are unlikely to cause immediate bronchial dilatation on account of the high pleural pressure they produce. Here, again, it must be recognized that pleural effusion and pneumothorax may both be secondary to atelectasis.⁹⁰ I met with an undoubted case of pleural effusion secondary to massive atelectasis,⁸⁷ though it is rarely possible to decide this question with any confidence in a particular case.

Collapse of the lung, due to fluid or air, is probably a rare cause of bronchiectasis, as complete reexpansion is the rule, even after three years, which is the usual duration of artificial pneumothorax. The rarity with which artificial collapse of the lung produces bronchiectasis is probably due to the absence of bronchial infection.

Certainly, reports of bronchiectasis following hydrothorax or pneumothorax are hard to find in the literature. Ballon, Singer and Graham¹³ mentioned pleural effusion as a cause of bronchiectasis, but it did not occur in their own series of 149 cases. Farrell⁴¹ and Findlay and Graham²⁹ recorded pleurisy as a cause in 2 cases, but did not mention effusion. A warning against accepting this alone as a cause of collapse has already been given. Failure of a compressed lung to reexpand or onset of infection during the period of compression could

88. Bradford, J. R.: *Quart. J. Med.* **12**:127, 1918.

89. Scott, W. J. M.: Postoperative Massive Collapse of the Lung, *Arch. Surg.* **10**:73 (Jan., pt. 1) 1925.

90. Burnham, A. C.: *Surg., Gynec. & Obst.* **19**:468, 1914. Escudero, L., and Adams, W. E.: Spontaneous Pneumothorax Associated with Massive Atelectasis: Experimental and Clinical Study, *Arch. Int. Med.* **63**:29 (Jan.) 1939.

lead to permanent bronchiectasis, but if either occurs it must be symptomless. It is therefore extremely unlikely that persistent collapse produces of itself permanent bronchiectasis, although an extensive bronchographic study would be required to clinch the matter.

Infection, and the consequent damage to the bronchial wall, seems to remain the deciding factor in the permanence of bronchial dilatation.

Empyema is mentioned in the literature as a cause of bronchiectasis in some instances, but it must be remembered that the lung in these cases is infected, and caution must be used in blaming the empyema itself.

Factors predisposing to atelectasis include partial bronchial obstruction and the various causes of inefficient aeration of the lung.

Partial bronchial obstruction obviously predisposes to collapse, because a complete bronchial block is much more likely to occur in a narrowed bronchial lumen. This is typically seen, in clinical experience, in those cases in which attention is drawn to the existence of a bronchial carcinoma by the occurrence of lobar or pulmonary collapse.

Chronic bronchial infection is a theoretic predisposing factor, but no direct evidence of its influence was found. Scott⁸⁹ found clinical evidence of preoperative bronchial infection in 6 out of 40 cases of postoperative atelectasis, but it does not appear that in these cases chronic infection existed. In an unpublished series of 53 cases of mine in which the patients were examined clinically and roentgenographically before and after abdominal operation, I found lobar or lobular collapse in 15 cases. In the 4 cases in that series in which preexisting bronchial infection could be diagnosed, however, there was no postoperative complication.

Inefficient aeration of a lobe or lung may be due to deficiencies of the respiratory apparatus or to faulty breathing.

Paralysis or inhibition of the diaphragm was proposed by Pasteur⁹¹ as the sole cause of collapse of the lungs in most cases. He found that in 7 out of 8 patients who died with diphtheritic paralysis, partial or complete collapse of a lower lobe was present at autopsy. In 2 patients the collapse was bilateral. Later⁹² he studied postoperative collapse and pointed out the severe inhibition of the diaphragm, which occurs particularly after operation on the upper part of the abdomen and which he considered as reflex. It is well known clinically that collapse occurs most frequently after operation in this region, a fact which supports his view. This theory is, however, largely discounted today in view of the clear evidence of infective obstruction presented by Jackson⁶ and others who have been cited. It remains likely, however, that inefficient aeration of the lung, such as occurs when the diaphragm is inhibited,

91. Pasteur, W.: *Lancet* 2:1351, 1908.

92. Pasteur, W.: *Lancet* 2:1910, 1910; *Brit. J. Surg.* 1:587, 1914.

will predispose to the occurrence of collapse. This fact was not denied by any author I was able to consult.

One might suppose that inhibition of costal breathing would also predispose to collapse if this is so, and dry pleurisy may, therefore, be mentioned as a possible, though unproved, predisposing factor.

Faulty breathing would appear to be another possible predisposing factor, though evidence of this, naturally, is absent. Thoracic breathing itself does not seem to act in this way. In the 15 cases of postoperative collapse which were just cited, I found that such collapse was as frequent in diaphragmatic breathers as in thoracic breathers. In fact, in 8 cases the patients were abdominal breathers and in 7 they were thoracic breathers.

2. *Causes of Parenchymal Damage or Destruction.*—The view that peribronchial destruction might cause dilatation of abnormal bronchi by weakening, in much the same way as collapse does, the normal support afforded to them by aerated lung tissue was previously expressed.

The causes of such damage or destruction are obvious. Bronchopneumonia, abscess and gangrene are examples, and the extensive peribronchial destruction that may occur in association with pneumoconiosis is another likely cause.

3. *Factors Favoring the Retention of Weighty Secretions within the Bronchi.*—Here, again, partial obstruction is the obvious cause, although the presence of severely damaged bronchi which have lost their tone altogether is itself a likely factor in the further retention of secretions.

As was already stated, the actual effect of the pressure of retained secretions is rather uncertain, but the possibility of its acting as a cause of abnormal bronchial strain cannot be ruled out.

CLINICAL FEATURES AND DIAGNOSIS

Much has been written on this subject, and the devotion of a section to it may, therefore, appear to be a work of supererogation. But in view of the relative, though perhaps decreasing, infrequency of the actual diagnosis, it was considered that a clinical review of the 68 cases was necessary.

The impression appears to be widespread and deeply rooted in the minds of the medical profession that bronchiectasis is something of a rarity. No statistical refutation of this idea is practicable, but that it is a complete, and most unfortunate, fallacy has been amply demonstrated by the large increase in the number of recognized cases since contrast roentgenography has been extensively applied to the study of bronchopulmonary disease. It is of interest to recall that this really extensive use of bronchography covers a period of not more than seven or eight

years, although the work of Sicard and Forestier⁹³ is now over eighteen years old. Before this, bronchiectasis could be diagnosed with certainty at autopsy only; in fact, comparatively few patients died in a hospital, since they were apt to be discharged as incurable after a period of medical treatment. Many persons no doubt died, as probably many still die, without admission to a hospital or observation by a physician. Furthermore, the clinical diagnosis, as has already been suggested, was largely a matter of presumption or suspicion. Thus, the period is, as yet, relatively short in which a new clinical conception of the disease could be formed.

In the present series of 68 cases, the average duration of symptoms before diagnosis was eleven years, and when one takes into account the average age of the patient, which was 17 years and 3 months, it is obvious that early diagnosis was not a feature. This duration appeared to be longer than that in other reported series, but since in the latter the average age was not given, comparison is unsatisfactory.

The patients were referred as possibly having tuberculosis or chronic bronchitis or with the comment "tuberculosis officer states that the patient is nontuberculous." Sixteen patients had spent longer or shorter periods in sanatoriums. Ochsner,²⁶ by the way, cited Hamilton as stating that 25 to 50 per cent of all inmates of tuberculosis sanatoriums are nontuberculous.

The following analysis of the present series of cases is therefore presented, without apology. No case has been met with in which persistent coughing, of varying severity, has not been an original symptom. In 39 cases (57 per cent) the cough dated from an acute illness of the respiratory tract, the details of which are to be seen in the accompanying tabulation.

Bronchopneumonia	22 cases	{ Primary 19 Measles 2 Pertussis 1
Lobar pneumonia	1 case	
Bronchitis	14 cases	{ Primary 7 Pertussis 4 Influenza 2 Rubella (?) 1
Aspiration of foreign bodies.....	2 cases	
Total		39 cases

In 43 per cent of my cases the onset was insidious and could not be related to any definite cause. Warner⁹⁴ found 41 per cent in which the onset was insidious. Ballou, Singer and Graham¹⁸ stated that bronchiectasis may be symptomless, and Fletcher,^{48a} in a series of 100 cases, reported absence of cough in 32 per cent. Farrell,⁴¹ however, found only 1

93. Sicard, J. A., and Forestier, J.: Bull. et mém. Soc. de chir. de Paris 46:463, 1922.

94. Warner, W. P.: Factors Causing Bronchiectasis: Their Clinical Application to Diagnosis and Treatment, J. A. M. A. 105:1666 (Nov. 23) 1935.

case out of 100 in which the presence of cough was not recorded, and Findlay and Graham,⁹⁰ 1 case only out of 25. Warner⁹⁴ and Rivière⁹⁵ appeared to regard coughing as a constant symptom. There is a certain discrepancy in these reports, but it is at least evident that coughing is an expected symptom. In 11 of my cases symptoms were said to have dated "from birth," and to have appeared insidiously, and in 12 cases the onset was during the first year. In 60 cases expectoration was an accompaniment of the cough, and in 40 of these the two commenced coincidentally. In 20 cases raising of sputum was first noticed at varying intervals after onset of the cough, and in 13 of these its appearance was "spontaneous." In the remaining 8 cases the bronchiectasis was apparently "dry," but in 1 case, that of an infant, large amounts of foul-smelling pus could be obtained by gastric lavage, and in another case, that of a boy of 10, copious expectoration followed bronchoscopic examination. In 2 other cases bronchoscopic examination revealed the presence of abundant pus in the bronchi, while in the other 4 cases bronchoscopic examination has not as yet been permitted. The observations in these 68 cases, therefore, do not make possible definite confirmation of the existence of "dry" bronchiectasis. It is perhaps significant that other reports of this condition are unconfirmed by bronchoscopic examination, as far as I have seen.⁹⁶ It seems possible that the number of cases of "dry" bronchiectasis might be materially reduced if a truly dry, or uninfected, bronchial system were made the criterion. It may be mentioned that expectoration was not always persistent and that "dry phases" were not infrequent. One may, perhaps, sum up the position fairly by saying that the clinical absence of sputum is perfectly compatible with a diagnosis of bronchiectasis, but is not proof that the bronchi in such a case are not heavily infected. Sputum was abundant, i. e., from 3 up to 20 ounces (85 to 565 Gm.) or more daily in 44 cases, and was definitely purulent in 41 of these. In 16 cases the amount was small or "moderate," i. e., less than 3 ounces (85 Gm.) daily, and was definitely purulent in 11. Sputum was fetid in only 18 cases, however, and it was evident that the mere duration of the period of expectoration was without influence in this respect, as the average duration in the 18 cases was six years only, as against an average of seven and one-half years for the 60 cases in which there was visible sputum. In only 2 cases did any change in the character of the sputum occur, and in neither could any obvious cause for this be elicited. In 1 case a mucous sputum became purulent after ten years, and in the other a purulent sputum became foul smelling after eighteen years. In all cases repeated examination failed to reveal the presence of tubercle

95. Rivière, C.: *St. Barth. Hosp. Rep.* **41**:123, 1905.

96. Wall, C., and Hoyle, J. C.: *Brit. M. J.* **1**:597, 1933. Burrell, R. S., and Traill, R.: *Lancet* **1**:182, 1930. Pinchin, A. J. S., and Morlock, H. V.: *Brit. M. J.* **2**:315, 1930. Moll.⁶⁵

bacilli. Indeed, no characteristic bacteriologic picture could be demonstrated. In only 7 cases was a definite history of contact with tuberculosis obtained, and in 1 of these the patient had previously been treated in a sanatorium. At autopsy this patient was found to have an old tuberculous lesion at the apex, with tuberculous bronchopulmonary nodes pressing on the bronchus leading to the middle lobe. This pressure had evidently caused bronchial obstruction. The series, therefore, with 1 exception, did not appear to illustrate the etiologic role of tuberculosis, the importance of which seems to have been amply proved by Cohen and Higgins,⁷² at Glen Lake Sanatorium, Oak Terrace, Minn., and by Vinson,⁸⁰ Bucher,⁷⁴ Andrews,⁷⁵ de Bruin⁸¹ and others. As has been mentioned, however, it is mainly as a cause of bronchial obstruction that tuberculosis acts, and this action is difficult to exclude during life.

Hemoptysis of any severity was noted in only 7 cases (10.3 per cent), although a history of staining of the sputum was elicited in 8 others. This incidence is low as compared with that in certain other series, but particular inquiry was always made and it is certain that the record is a true one.

Thorpe⁹⁷ reported hemoptysis in 27 of 53 cases, and Acland⁹⁸ obtained a history of blood spitting in 12 of 25 cases and of staining of the sputum in 8 other cases. Ochsner²⁶ stated that hemoptysis occurred in 50 to 70 per cent of his cases, and Ballou, Singer and Graham¹³ remarked that it "is more frequent in bronchiectasis than it is in tuberculosis." Farrell⁴¹ and Fletcher,^{48a} however, both gave lower values for the incidence of hemoptysis (42.8 and 6 per cent, respectively), Fletcher's figure being based on 100 cases. Warner⁹⁴ noted hemoptysis in 45 per cent of 110 cases and Hedblom in about 50 per cent of all cases.²⁴ It is likely that those authors whose work keeps them in close touch with cases of tuberculosis will meet with a greater number of instances of hemoptysis.

Wheezing, either persistent or occurring in asthmatoïd attacks, was a prominent symptom in 10 cases (15 per cent). Three of these were first referred as cases of asthma, and the long-standing existence of cough and sputum was admitted only on inquiry. The symptom appears to have no importance except as a possible cause of diagnostic error, a mistake which should not occur. All 3 "asthmatic" patients gave a history of abundant purulent expectoration, and presented definite clubbing of the fingers and toes. It is, however, true that other authors appear to have been impressed by these asthmatic symptoms, for they mention asthma as a cause of bronchiectasis!

Except in the 10 cases just mentioned, breathlessness was not a feature, and in 50 of the remaining 58 cases the patients were able to

97. Thorpe, E. S., Jr.: *Am. J. M. Sc.* **177**:759, 1929.

98. Acland, T. D.: *Practitioner* **1**:379, 1902.

lead an active life. Eight patients were in poor general health and were forced to lead a semi-invalid existence. A history of nasal symptoms was elicited in 10 cases, though only on direct inquiry. In 8 of these, and in 5 others in which the patients denied any nasal trouble, sinusitis was found to exist. This is a lower incidence than certain authors have found, and it is not denied that sinusitis may have been overlooked in some cases. This matter is referred to in the section on etiology. The nasal symptoms were persistent "stopped nose" and intermittent nasal discharge.

A characteristic and not infrequent clinical feature of bronchiectasis is the recurrence of acute febrile exacerbations, in which symptoms and signs are temporarily increased. These illnesses are usually short lived, lasting for three or four days as a rule, but are severe and in many cases are referred to by the patient or his relatives as "pneumonia." Indeed, the appearance of the patient, who is often acutely ill and toxic, with high temperature and increased respiration and cyanosis, may closely simulate that of bronchopneumonia, and patches of tubular breathing and crackling crepitations are not infrequently noted. The short duration of the illness and the rapid recovery of the patient, who is rarely in bed for more than a week or ten days, put such a diagnosis out of count. Furthermore, the history of previous similar illnesses and of persistent symptoms in the intervals reveals the true nature of the complaint. Twenty-five cases of the 68, or 36.8 per cent, were typical instances of this syndrome. Fletcher ^{48a} reported recurrent febrile exacerbations in 28 per cent of his 100 cases, but other authors did not give definite figures.

In 39 cases, or 57.3 per cent, definite clubbing of the fingers and toes was present, though in varying degree. As the accompanying tabulation shows, clubbing was relatively more frequent in patients with purulent sputum and most frequent in those with fetid sputum. However, clubbing may be absent in a patient with fetid expectoration and may be present in another with only moderate mucous sputum or in one with no visible sputum whatever.

Incidence of Clubbing of the Fingers and Toes

	No. of Patients	No. with Clubbing
Purulent nonfetid bronchorrhea.....	38	20
Purulent fetid bronchorrhea.....	18	15
Mucous bronchorrhea	8	3
Absence of sputum (no bronchoscopic examination)...	4	1

The mere duration of visible expectoration appeared to bear no relation to the incidence of clubbing. The average duration in the 39 cases in which digits were clubbed was seven and one-half years, which is exactly the average in the 60 cases in which there was visible sputum.

As has been stated, 60 of the 68 patients (88 per cent) had good general health. Twenty-eight patients, however, were definitely underweight, and most of those whose symptoms dated from infancy, i. e., 45 patients, or 66 per cent, were somewhat undersized.

Tonsillar infection was not a prominent feature. Six patients had suffered tonsillectomy, and 20 per cent of the remaining patients had some tonsillar infection. This was never gross, and the percentage cannot be considered significant in a group the majority of whom had been expectorating purulent or foul material for years. Such tonsillar infection as was present could not be shown to bear any relation either to the general health or to the severity of the symptoms.

Physical Signs.—Much is made in the literature of the frequency with which physical signs are absent or elusive in cases of bronchiectasis. The present series, although perhaps not large enough to furnish conclusive evidence, certainly gives no support to this view. Definite signs were completely absent in only 1 case, although in 1 other the only sign noted was local deficiency of expansion. Furthermore, physical signs, when present, were persistent, though varying in intensity from time to time.

Signs of which particular note was made were deficient expansion, impairment of the percussion note, abnormality of the breath sounds, presence of adventitious sounds and displacement of the cardiac apex beat. In no less than 63 of the 67 cases in which physical signs were detected, three or more of these five signs were noted.

Incidence of Local Signs in 67 Cases

Deficient expansion	54
Abnormal breath sounds.....	59
(Diminished 42, bronchial 17)	
Impairment of percussion note.....	56
(Impairment amounting to dulness, 20)	
Adventitious sounds: Crackling rales	56
Rhonchi	25
Displacement of the apex beat.....	21

In cases of atelectasis of the lower lobe of the lung, the sign not infrequently observed was impairment of the percussion note at the base of the lobe, which was most marked close to the spine and diminished as the axilla was approached. There were other signs limited to this area. The outline of the area of dulness or impairment in these cases was exactly the reverse of that so often noted in cases of pleural effusion.

In summing up the significance of these observations, it is justifiable to suggest that although the absence of physical signs by no means excludes bronchiectasis, it is in itself evidence against the presumptive diagnosis.

It is to be regretted that no record was kept of those cases in which a suggestive history led to the making of a bronchogram in the absence of physical signs. The number was not inconsiderable, however, and the consistently negative results were impressive. It is, of course, important that bronchiectasis should not be overlooked, particularly in children, in whom the prospect of successful treatment is so much brighter than in adults, and it is fully realized that negative bronchograms will continue to be inevitable. But, with care and discrimination in the assessment of the clinical and roentgenologic features in each case, it is felt that the number in which the patient is subjected to a bronchographic examination, with negative results, could be appreciably reduced. The risks of the procedure are slight, but with children a general anesthetic is always necessary, and I have met with 2 cases in which some anxiety was felt during the operation. In cases of unexplained hemoptysis and in cases in which there are suggestive clinical or roentgenologic signs, bronchographic examination is necessary, and no suggestion against it is intended. In the absence of such features, however, it is evident from this series that a history of an unexplained cough alone is an inadequate indication for bronchographic examination.

The sole case in the present series in which clinical signs were wholly lacking was one of unexplained hemoptysis in a young girl, and in her case the ordinary roentgenogram revealed a well marked irregular mottling of the basal region of the left lung, which extended far beyond the heart shadow. No case was observed in which definite clinical or roentgenologic evidence was absent before the use of contrast roentgenograms.

It is hoped that the impression has not been conveyed that the presence of physical signs is, in my opinion, diagnostic of bronchiectasis. As has been indicated, cases are met with in which a typical history and characteristic signs are associated with a normal bronchogram. Such cases, of course, require investigation, and, indeed, the patients should probably be reexamined at a later date, particularly if signs and symptoms persist. The evidence which was brought forward in the section on pathogenesis and pathology and the work of Roles and Todd on the "spread" of bronchiectasis give point to this suggestion.

The clinical study of a series of 68 cases of bronchiectasis has led to the conclusion that the disease is one which is usually associated with definite symptoms and physical signs and that any tendency toward indiscriminate bronchographic examination is to be deprecated.

Bronchiectasis in Infancy and Childhood.—In 29 of the 68 cases the patient was 12 years of age or under when first seen, and 3 of them were under the age of 2. In 2 of the infants under 2 years the roentgenologic changes were those described as characteristic of "congenital cystic disease of the lung," although the clinical features were not significantly

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Tonsillar infection was not a prominent feature. Six patients had suffered tonsillectomy, and 20 per cent of the remaining patients had some tonsillar infection. This was never gross, and the percentage cannot be considered significant in a group the majority of whom had been expectorating purulent or foul material for years. Such tonsillar infection as was present could not be shown to bear any relation either to the general health or to the severity of the symptoms.

Physical Signs.—Much is made in the literature of the frequency with which physical signs are absent or elusive in cases of bronchiectasis. The present series, although perhaps not large enough to furnish conclusive evidence, certainly gives no support to this view. Definite signs were completely absent in only 1 case, although in 1 other the only sign noted was local deficiency of expansion. Furthermore, physical signs, when present, were persistent, though varying in intensity from time to time.

Signs of which particular note was made were deficient expansion, impairment of the percussion note, abnormality of the breath sounds, presence of adventitious sounds and displacement of the cardiac apex beat. In no less than 63 of the 67 cases in which physical signs were detected, three or more of these five signs were noted.

Incidence of Local Signs in 67 Cases

Deficient expansion	54
Abnormal breath sounds.....	59
(Diminished 42, bronchial 17)	
Impairment of percussion note.....	56
(Impairment amounting to dulness, 20)	
Adventitious sounds: Crackling rales	56
Rhonchi	25
Displacement of the apex beat.....	21

In cases of atelectasis of the lower lobe of the lung, the sign not infrequently observed was impairment of the percussion note at the base of the lobe, which was most marked close to the spine and diminished as the axilla was approached. There were other signs limited to this area. The outline of the area of dulness or impairment in these cases was exactly the reverse of that so often noted in cases of pleural effusion.

In summing up the significance of these observations, it is justifiable to suggest that although the absence of physical signs by no means excludes bronchiectasis, it is in itself evidence against the presumptive diagnosis.

It is to be regretted that no record was kept of those cases in which a suggestive history led to the making of a bronchogram in the absence of physical signs. The number was not inconsiderable, however, and the consistently negative results were impressive. It is, of course, important that bronchiectasis should not be overlooked, particularly in children, in whom the prospect of successful treatment is so much brighter than in adults, and it is fully realized that negative bronchograms will continue to be inevitable. But, with care and discrimination in the assessment of the clinical and roentgenologic features in each case, it is felt that the number in which the patient is subjected to a bronchographic examination, with negative results, could be appreciably reduced. The risks of the procedure are slight, but with children a general anesthetic is always necessary, and I have met with 2 cases in which some anxiety was felt during the operation. In cases of unexplained hemoptysis and in cases in which there are suggestive clinical or roentgenologic signs, bronchographic examination is necessary, and no suggestion against it is intended. In the absence of such features, however, it is evident from this series that a history of an unexplained cough alone is an inadequate indication for bronchographic examination.

The sole case in the present series in which clinical signs were wholly lacking was one of unexplained hemoptysis in a young girl, and in her case the ordinary roentgenogram revealed a well marked irregular mottling of the basal region of the left lung, which extended far beyond the heart shadow. No case was observed in which definite clinical or roentgenologic evidence was absent before the use of contrast roentgenograms.

It is hoped that the impression has not been conveyed that the presence of physical signs is, in my opinion, diagnostic of bronchiectasis. As has been indicated, cases are met with in which a typical history and characteristic signs are associated with a normal bronchogram. Such cases, of course, require investigation, and, indeed, the patients should probably be reexamined at a later date, particularly if signs and symptoms persist. The evidence which was brought forward in the section on pathogenesis and pathology and the work of Roles and Todd on the "spread" of bronchiectasis give point to this suggestion.

The clinical study of a series of 68 cases of bronchiectasis has led to the conclusion that the disease is one which is usually associated with definite symptoms and physical signs and that any tendency toward indiscriminate bronchographic examination is to be deprecated.

Bronchiectasis in Infancy and Childhood.—In 29 of the 68 cases the patient was 12 years of age or under when first seen, and 3 of them were under the age of 2. In 2 of the infants under 2 years the roentgenologic changes were those described as characteristic of "congenital cystic disease of the lung," although the clinical features were not significantly

different from those in the other children. This diagnosis was, unfortunately, not verified by autopsy, as both these patients died at home. Whether or not these infants had, in reality, a congenital bronchial anomaly, theirs are the only cases of bronchiectasis in children which differ in any respect from the cases in adults. Further reference to congenital cystic disease and to bronchiectasis in childhood will be made when a classification of the cases is made, but it may be stated here that no evidence which in any way justifies the consideration of children suffering from bronchiectasis as a separate group was discovered from a careful study of the present series.

Sauerbruch⁹⁹ gave it as his opinion that in all cases of bronchiectasis in children in which the disease is confined to one lobe the condition is congenital in origin, and so-called congenital cystic disease of the lung has been reported as occurring rather more frequently in children.^{35b} Furthermore, a number of authors reported series of cases of bronchiectasis in childhood, among them Boyd,¹⁰⁰ Anspach,¹⁰¹ McNeil, MacGregor and Alexander,²² Findlay and Graham²⁹ and Ellis.¹⁰²

Such reports, although the authors did not state, and apparently had no intention of suggesting, that bronchiectasis in childhood should be studied apart from bronchiectasis in general, may yet create an impression to this effect. The study of the present series led me to conclude that there was nothing to be gained by the adoption of such an attitude, and it was for this reason that this section was written.

The real importance of discovering bronchiectasis in a child is the fact that treatment, especially surgical treatment, is so much more likely to be effective in the child and carries with it a much smaller risk.

ROENTGENOLOGIC FEATURES

Roentgenographic Survey of Present Series.—The preceding clinical summary has provided evidence of the importance of careful physical examination in the presumptive diagnosis of bronchiectasis. It is generally agreed, however, that physical examination alone is insufficient for the positive recognition of the disease. Roentgenographic and bronchographic examinations are essential for this purpose and for the further determination of the extent of the damage. It is therefore necessary to survey the roentgenologic observations in the 68 cases.

I did not find in the literature any statistical record of the roentgenographic features of this disease, except with regard to the frequency of

99. Sauerbruch (footnotes 17 and 39).

100. Boyd, G. L.: *Canad. M. A. J.* **25**:174, 1931.

101. Anspach, W. E.: *Atelectasis and Bronchiectasis in Children: Study of Fifty Cases Presenting Triangular Shadow at Base of Lung*, *Am. J. Dis. Child.* **47**:1011 (May) 1934.

102. Ellis, R.: *Arch. Dis. Childhood* **8**:25, 1935.

"atelectatic" shadows. General statements as to the changes which may be expected were, however, usual. Thus, it was said that the picture may be normal in a great many cases or that peribronchial "streakiness" alone may be seen. In certain cases more pronounced "scarring" was shown, occasionally with cavitation. In others, again, triangular, wedge-shaped shadows, which were usually basal but may be seen elsewhere, were reported. The frequency of these triangular shadows, which were shown by Comby¹⁰³ and Singer and Graham¹⁰⁴ to be due to local pulmonary collapse rather than to mediastinal effusions, has been variously estimated, but will be discussed later in this section. Finally, the heart was not infrequently seen to be displaced toward the diseased side.

All of these features were noted in the present series. Anteroposterior and, in the majority of cases, lateral views were taken, both before and after the injection of iodized poppy seed oil. The lateral view was helpful in many cases in determining or confirming the exact situation and extent of the lesion and is probably advisable as a routine. It is particularly in the diagnosis of bronchial dilatation in the middle lobe of the right lung and in the lingula of the upper lobe of the left lung (that portion aerated by the lower branch of the bronchus serving the upper lobe) that the lateral view is of value.

The following tabulation summarizes the observations in the present series of 68 cases.

Pathologic Changes Seen Roentgenologically

Local "fibrosis" (well marked, irregular shadowing).....	30
Atelectasis (triangular shadow).....	27
Cystic appearance (definite multiple cavities).....	3
General opacity (massive collapse, with appearance of cavities)...	2
No obvious abnormality, or mere "streaky" bronchial shadows...	6
	68

There are two striking features in this tabulation. The first is the small number of normal roentgenograms, and the second is the large number of atelectatic shadows noted.

It is generally stated that a normal roentgenologic appearance is common in cases of bronchiectasis, although exact figures are not given.¹⁰⁵ Farrell,⁴¹ however, reported roentgenographic changes in all of 100 cases. Warner⁹⁴ found only 17 instances of atelectasis in 110 cases, and Fletcher, only 20 in 100 cases. The diagnosis in my series was, however, definitely confirmed by bronchographic examination in 62 cases. Here, again, however, it must be stated that "fibrotic" mottling is not infrequently seen in cases in which no bronchial dilatation can be demon-

103. Comby: Bull. Soc. de pédiat. de Paris **23**:385, 1925.

104. Singer, J. J., and Graham, E. A.: J. Missouri M. A. **19**:390, 1922.

105. Hedblom.²⁴ Singer and Graham.¹⁰⁴

strated. Bronchograms were accepted as the final diagnostic criterion in my series, although it now seems possible that in the future tomographic examination will also play a part. Davidson¹⁰⁶ showed me a beautiful demonstration of bronchial dilatation by this means, and Kerley¹⁰⁷ claimed to be able to diagnose bronchiectasis roentgenographically in many cases. Little difference in the result was observed by different methods, though better definition was perhaps obtained when the patient was under general anesthesia, which was employed in all cases of children. Iodized poppyseed oil was injected through the endotracheal tube in such cases. The other methods used were injection through the cricothyroid membrane and introduction by means of a nasal catheter.

In 3 cases of young infants, all of which were instances of gross cystic changes in the lung, bronchographic examination was considered inadvisable, but the roentgenograms were highly characteristic and the diagnosis was thought to be justified.

No attempt was made to classify the cases according to the shape of the bronchial dilatations as outlined by iodized poppyseed oil, though all the varieties described in the literature were seen. No etiologic or pathologic basis has been demonstrated to justify such a classification. In general, it appeared that a saccular appearance was perhaps associated more particularly with advanced disease, but as the treatment of any given patient was based more on the clinical condition and the bronchoscopic evidence than on the morphologic character of the bronchi, it appeared that nothing was to be gained from any such classification.

In 62 of the 65 cases in which bronchograms were made the diagnosis was immediately apparent. In 2 cases the diagnosis was disputed, even after repeated bronchograms were made, but was confirmed by subsequent operation and pathologic study. In the remaining case the diagnosis was based on the close similarity of the roentgenographic picture to that in the other 2 cases. The exact extent of the disease was not so readily determined, however, and it is possible that several mistakes were made.

Doubt and difficulty arose in several cases as to the involvement of the lingula of the upper lobe of the left lung and of the middle lobe of the right lung. Many thoracic surgeons hold that when the lower lobe of the left lung is involved the lingula is usually diseased also. In my series the lingula was clearly recognized as diseased in association with the lower lobe of the left lung in only 10 cases, whereas in 25 cases the lower lobe of the left lung appeared to be diseased but not the lingula. In 3 of these 35 cases bronchographic examination subsequent to operation revealed changes in the lingula, and in 19 the lingula was normal. In 13 cases no operation has as yet been performed. No case of apparent

106. Davidson, S. W.: Personal communication to the author.

107. Kerley, P.: *Brit. J. Radiol.* 5:234, 1932.

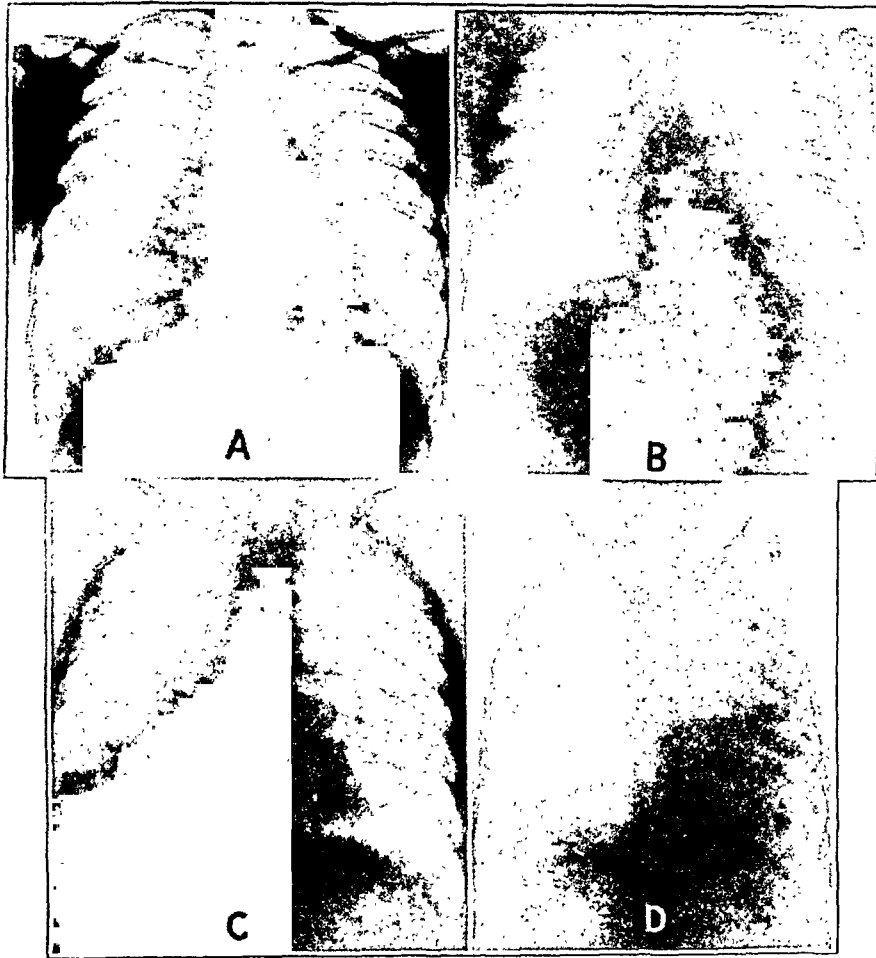


Fig. 16.—*A*, "fibrotic" mottling at the bases of both lungs. *B*, atelectatic appearance of the lungs. Note the dense triangular shadow within the heart shadow. *C*, cystic appearance of the lungs. Note the multiple cavities throughout the lower zones of both lungs. *D*, general opacity of the left pulmonary field. Note the displacement of the heart and trachea to the left.



Fig. 17.—Normal appearance of the lungs and bronchi.

error with regard to the diagnosis of involvement of the middle lobe of the right lung has yet been demonstrated in this way, although doubt sometimes existed.

The possibility that dilatation was in fact not present at the first examination, but developed later, consequent to physical changes within

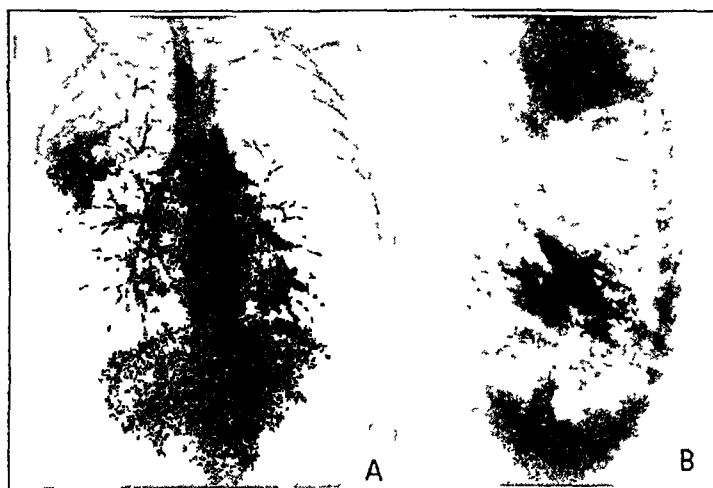


Fig. 18.—*A*, bronchogram in a case in which the diagnosis of bronchiectasis was in dispute for some time, but was confirmed by examination of the excised lung. *B*, bronchogram taken in the lateral view (same case). Note the evidence of lingular dilatations.

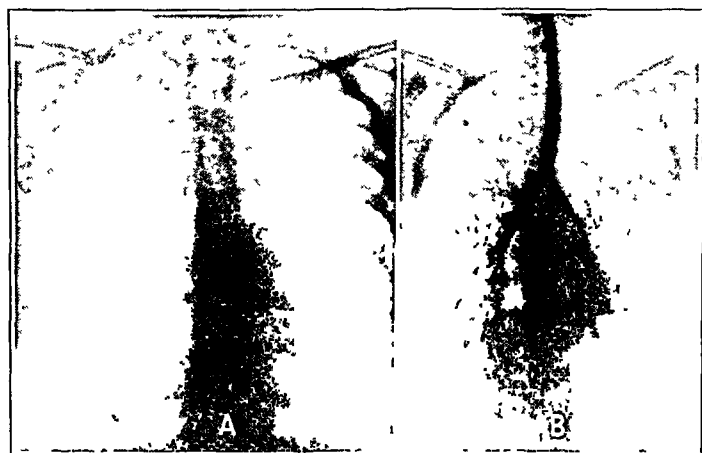


Fig. 19.—*A*, an atelectatic shadow. *B*, the lower lobe and the lingula of the left lung are involved. The bronchi of the lower lobe are crowded within an atelectatic shadow. The lingula, even though the bronchi are crowded, casts no shadow.

the thorax produced by the operation, must be borne in mind. The conclusion arrived at in the section on pathogenesis regarding diseased bronchi potentially liable to dilatation and the work of Roles and Todd ¹⁰⁸

108. Roles, F. C., and Todd, G. S.: *Brit. M. J.* 2:639, 1933.

on the "spread" of bronchiectasis lend point to this suggestion. No proof, however, can be offered.

Experience with these doubts and difficulties leads to the conclusion that the taking of both anteroposterior and lateral roentgenograms of each lung separately is necessary in each case, and latterly this has been done. But in the majority of cases ignorance of the necessity of this practice, and certain other causes, prevented its adoption. One hindrance to the general adoption of unilateral bronchographic examination is likely to be the large number of such procedures performed, which is a further argument in favor of their reduction when not indicated.

In 1 case, the lingula alone showed definite dilatations, and that in the lateral view only. The bronchi leading to the lower lobe were apparently

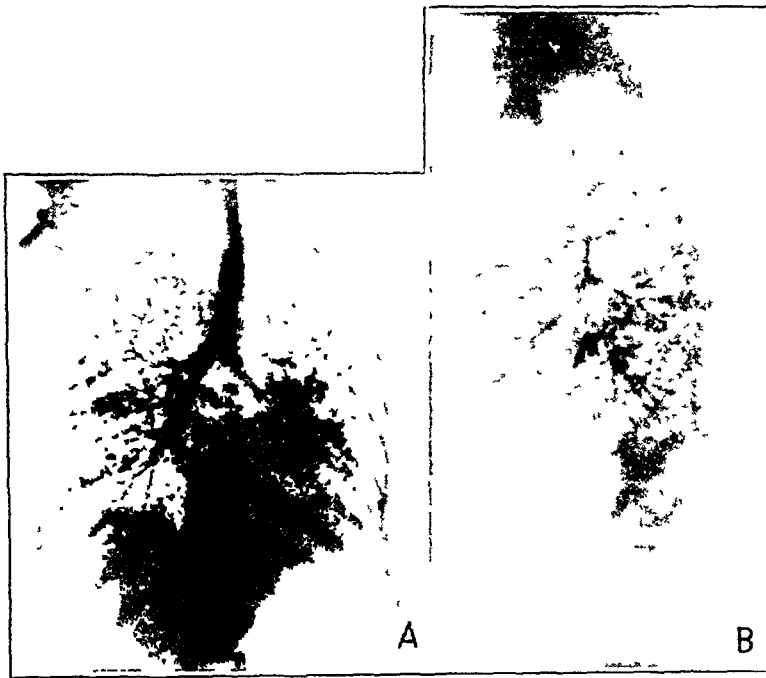


Fig. 20.—*A*, a case in which the anteroposterior view showed no clear evidence of dilatation. *B*, dilatation of the lingular branches, as seen in the lateral view. (Later, the bronchi of the lower lobe became obviously dilated.)

normal, but dilatations were demonstrated later, and the lobe was removed at a second operation.

One further technical point may be mentioned. Ochsner²⁶ claimed to have demonstrated dilatations in cases in which the alveoli rapidly became filled with iodized poppyseed oil, obscuring the bronchi. He urged injection of iodized oil under the fluoroscopic screen, stating that within a few minutes the bronchi may be obscured and bronchiectasis missed. This difficulty was not serious in any case in my series, and the matter has not been mentioned by other authors. In 1 case the bronchi were observed in the anteroposterior view, but were clearly shown in the lateral view. The danger of error can be eliminated by avoiding the use

of too much iodized oil. When the normal maximum dose of 20 to 30 cc. (5 to 10 cc. for children) is used, it is seen that a characteristic feature of bronchiectasis is the failure of the iodized oil to enter the alveoli at all in the diseased area, whereas it enters readily when the bronchi are normal.¹⁰⁹ Personally, I regard a bronchogram with suspicion, even if the bronchial caliber appears roughly normal, when the alveoli are not entered.

Apparent Situation and Extent of Bronchiectasis in the 65 Cases in Which Bronchograms Were Made

Unilateral	53	{ Left	37
		{ Right	16
Bilateral	12		
Unilobar	38	{ Lower lobe, left lung.....	25
		{ Lower lobe, right lung.....	11
		{ Middle lobe, right lung.....	1
		{ Upper lobe, right lung.....	1
Multilobar	27	{ 2 lobes affected.....	22
		{ 3 lobes affected.....	5

The features to which especial attention may be drawn are the following: the preponderance of left-sided disease in instances of unilateral disease, which accords with general experience; the relative frequency of multilobar disease, and the fact that only 1 case of apical bronchiectasis was met with. Apical bronchiectasis is liable to occur particularly in cases of tuberculosis, and the fact that proved tuberculosis was present in only 1 case in my series (one of bronchiectasis of a middle lobe) may account for the low incidence of apical bronchiectasis.

The conclusions which may be drawn from this roentgenologic survey seem to be as follows:

1. Bronchograms are readily diagnostic in the great majority of cases, but if doubt exists, particularly if the iodized oil fails to enter the alveoli, reexamination is indicated. If doubt still exists, the case must be reconsidered as a whole before bronchiectasis is excluded.

2. The determination of the extent of the disease may be difficult, but is likely to be materially assisted by unilateral bronchographic examination of the lungs. Lateral views are valuable.

3. The proportion of normal roentgenograms was somewhat lower than that in other reported series.

Atelectatic Bronchiectasis: Roentgenologic Diagnosis.—This subject requires especial note, both because of its great prominence in the present series and because of recent theories, previously mentioned, of the role of collapse in the production of bronchiectasis. In the section on classification atelectatic bronchiectasis will be treated as a whole. Here it is intended merely to discuss the roentgenologic criteria of its diagnosis.

109. (a) Warner, W. P.: *Canad. M. A. J.* **27**:589, 1932. (b) Findlay and Graham.²⁹

Roentgenologically, the atelectatic lobe typically appears as a dense homogeneous shadow, having the shape of a right-angled triangle, with the base on the diaphragm and the long side directed laterally and upward. Medially, the triangle merges with the heart shadow on the right side, and on the left side the whole shadow usually lies within the heart shadow, and some care is necessary to distinguish it. This description applies to the anteroposterior view of atelectasis of the lower lobe involvement of the middle lobe of the right lung. In the lateral view the middle lobe of the right lung is seen as a triangular wedge with its base against the sternum, while the lower lobe of the right lung has its base against the diaphragm.¹¹⁰ The shadow, in the lateral view, assumes a roughly rectangular shape if both the lower and the middle lobe are collapsed.

The lower lobe is much the most frequently involved, but in cases of tuberculosis or of bronchial carcinoma the upper lobe is frequently affected in this way. A triangular wedge then occupies the extreme apical region, with the base directed laterally.

Bronchographic examination demonstrates dilatation of the bronchi, which are crowded together within the dense shadow of the collapsed lobe. The lobe, which can thus be compared with that of the other side, is seen to be greatly shrunk, and the bronchi of the remaining lobe or lobes are observed to occupy the rest of the pulmonary field.

The heart may be displaced toward the affected side in cases of unilateral disease, but this is not universal; indeed, it was noted in only 8 of the 23 such cases in this series. Compensatory emphysema or fixation of the mediastinum appeared to be the reason for the absence of displacement of the heart in the others.

In cases of massive pulmonary atelectasis there is evident on the diseased side a general opacity, which is homogeneous, although cavities may be seen within it occasionally, as in 1 case in this series. The heart is displaced. Two cases illustrated this phenomenon, which has been fully described by Warner.^{109a} It is now necessary to consider whether the present accepted roentgenologic criteria of atelectasis require any extension or modification.¹¹¹ It will perhaps have been noticed that cardiac displacement was observed in 11 cases in which the recognized requirements for the diagnosis of atelectasis were not satisfied. A study of these cases showed that in 10 the roentgenographic appearance was that of "fibrosis." In the other case the roentgenogram was completely normal. The bronchogram in all cases revealed dilatation and some crowding. Furthermore, in a case of atelectatic bronchiectasis of the lower lobe of the left lung, the lingula of the upper lobe was also affected, although outside the triangular shadow. Lander¹¹¹ showed me the roentgenograms in a case of hemoptysis of unknown origin. In the

110. Gill, A. M., and Pearson, J. E. G.: *Arch. Dis. Childhood* 2:87, 1936.

111. Lander, F. P. L.: Personal communication to the author.

roentgenogram no abnormality was to be seen, but the bronchogram revealed gross dilatation and crowding of the bronchial tubes leading to the upper lobe of the right lung, so that they occupied a definitely smaller area than the normal. The bronchi of the middle and lower lobes occupied the remainder of the pulmonary field. Here was an instance of a shrunk lobe, containing crowded, dilated bronchi, which yet cast no shadow in the roentgenogram.

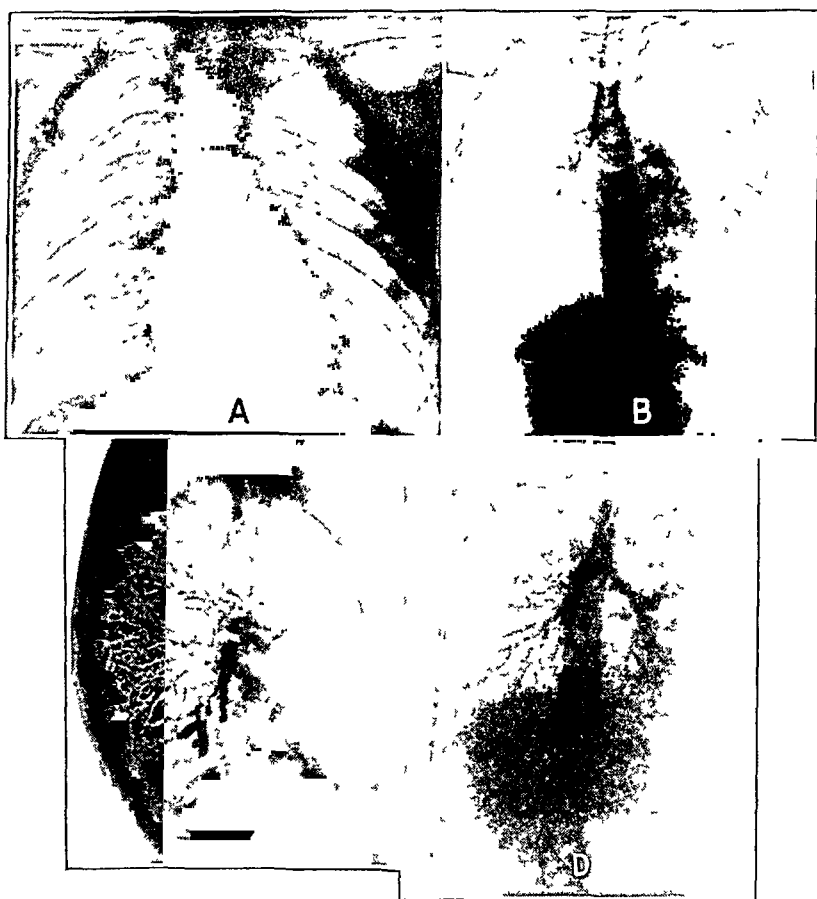


Fig. 21.—*A*, normal appearance of the lungs. No atelectatic shadow is visible. *B*, atelectatic bronchiectasis. Note the restriction of dilatations to the lower lobe and the crowding of the bronchi. *C*, lateral view (from same case as that from which *B* was taken). Note that the rest of the pulmonary field is occupied by the expanded upper lobe. There is a slight suggestion of dilatation of a lingular branch. *D*, massive atelectatic bronchiectasis.

The possibility is suggested that bronchiectasis may occur in lobular areas of collapse which are of insufficient size and density to produce a homogeneous shadow, or even in some cases to produce a shadow at all.

Mason¹¹² informed me that it is not infrequent at operation to recognize in the unhandled bronchiectatic lobe firm, purple patches, an observation which lends support to my suggestion.

112. Mason, G. A.: Personal communication to the author.

More evidence is required before this idea can be accepted, but it is put forward here as worthy of consideration and further investigation. If it were shown to be correct, it would certainly increase the importance to be ascribed to the role of pulmonary collapse in the production of bronchiectasis.

Bronchoscopy.—I did not perform the bronchoscopic examination in this series, but the results of others have tended to show that this procedure is of value as a guide to the surgeon in his decision whether to operate rather than as a diagnostic aid. The value of bronchoscopy in the treatment of bronchiectasis is not now seriously considered, except in cases of relatively recent atelectasis. Only a negligible amount of secretion can be aspirated in this way as compared with the copious amounts obtained in cases of massive atelectatic bronchiectasis by postural coughing and breathing exercises.

The case of the patient referred to in the section on pathogenesis (page 417) illustrates this point. Postural drainage and breathing exercises were instituted and produced definite improvement in the physical signs, with partial return of the heart's apex toward its normal position. Bronchoscopic examination was then performed and a small amount of tenacious mucopurulent material aspirated. This examination was followed by the introduction of iodized oil, which revealed a normal bronchial tree. The physical signs indicated a return to normal conditions. Jackson^{70a} emphasized the value of bronchoscopy in the treatment of such condition and his opinion is to be respected. In the case reported here, however, it seems that postural coughing and adequate physical exercises went far toward producing a cure before a bronchoscopic examination was carried out.

CLASSIFICATION

The classification of bronchiectasis is not a simple problem, and its solution has not been advanced by the development of a wide literature, owing to the absence of correlation of the clinical and roentgenologic findings with the morbid anatomic changes.

Reasons for doubting the value of any classification based on the morphology of the affected bronchi as shown in the bronchogram have been given in the preceding section. The conclusion was reached that the morbid anatomic appearance in the 28 cases in which material was available provided the only sound basis for classification.

The complete records of the patients in these cases were then examined again, and the excised lobes divided into two groups according to the morbid microscopic anatomy, as already described in the section on pathogenesis.

A detailed analysis of all the recorded observations in both the atelectatic and the bronchopneumonic group was made, and it appeared that the only satisfactory criterion for a classification was the bronchogram.

In the atelectatic group definite crowding of the affected bronchi was noted, and the lobe or lobes concerned were seen to occupy a much smaller part of the pulmonary field than normal. The unaffected lobe or lobes were observed to be expanded, apparently in order to compensate

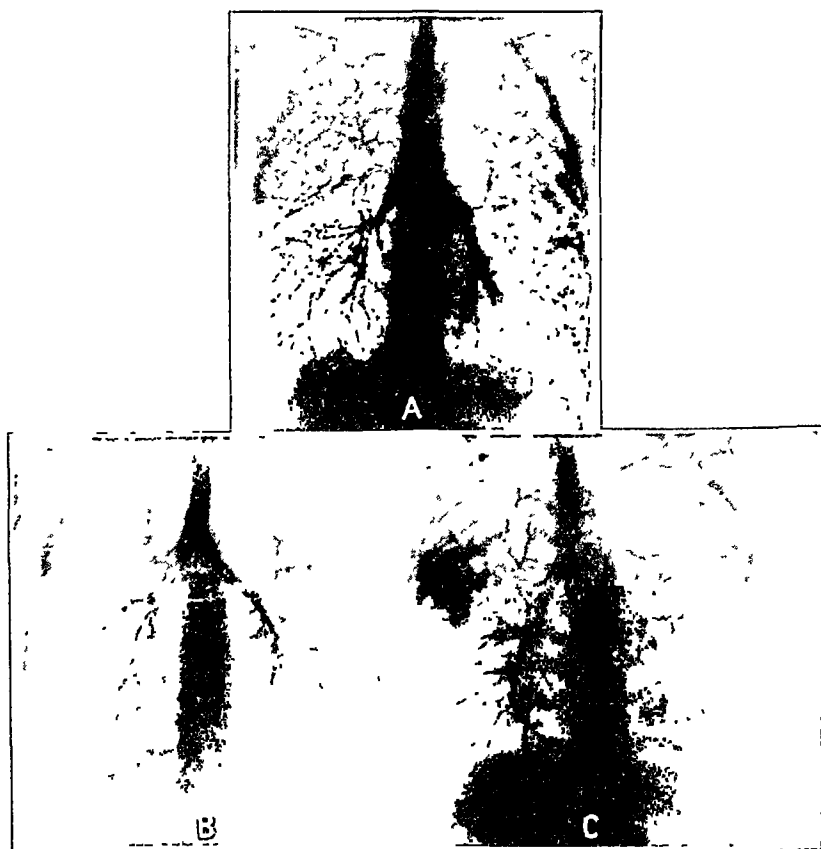


Fig. 22.—*A*, a bronchogram in which cylindric dilatations are visible at the base of the left lung. The bronchi of the lower lobe are crowded, and the upper lobe occupies by far the greater part of the pulmonary field. *B*, a bronchogram showing a normal bronchial tree. *C*, a bronchogram in a case of atelectatic bronchiectasis in which bronchial crowding was absent.

for this shrinkage. In 11 of the 18 cases of the atelectatic form there was neither cardiac displacement nor contraction of the chest wall, which shows how complete this compensatory expansion may be.

In the bronchopneumonic, or, better, the bronchogenic, group, on the other hand, there was no evidence of crowding of affected bronchi, and no abnormal bronchial distribution was present.

In 1 case only out of the 28 did this method of classification appear to fail.

In this case, that of a girl of 4, the lower lobe of the left lung was removed at operation and was found to be the seat of extensive collapse and of pronounced bronchial and peribronchial destructive change.

The lobe was also definitely, though moderately, shrunken. The roentgenogram showed fibrotic mottling, and the bronchogram, although it revealed moderate cylindric dilatations, was free of any evidence of crowding or of abnormal bronchial distribution. It is obvious that without examination of the actual lobe this case would have been classified under the bronchopneumonic type, and it must be admitted that this error is likely to occur occasionally. The reverse error, however, is unlikely to occur, and it is not considered that this exceptional case invalidates the proposed method of classification. Doubt and difficulty arise from time to time in the diagnosis of bronchial dilatation by bronchographic examination, but this is not held to destroy the value of the contrast roentgenogram in the diagnosis of bronchopulmonary disease.

It is likely that cases will occur which should be placed in a "combined" group. That is to say, a patient may have atelectatic bronchiectasis in one lobe and a bronchopneumonic type of change in another. The classification is really one of lobes rather than of cases.

Finally, reference must be made to a case reported by Sparks.¹¹³ It was that of a patient of 22 who was found to have a triangular shadow at the base of the left lung. The right lung was injected with iodized poppyseed oil, and the bronchi were found to be normal, but it was noticed that the triangular shadow had disappeared. The left lung was then injected, and well marked bronchial dilatations were shown at the base, although the atelectatic shadow was no longer present. This case was cited as proof that atelectasis may be an incident in the course of previously established bronchiectasis. The possibility that this occurs is in no way disputed here, but the absence of bronchographic evidence of a "preatelectatic" state in Sparks's case detracts from its value as a proof. The frequency of collapse in established bronchiectasis, if it occurs, cannot be estimated, but as no undoubted case has been reported, as far as is known, it is unlikely to be of serious significance. What is more likely is that reexpansion or partial reexpansion of an atelectatic lobe occurs, but that bronchial damage has already insured the permanency of the dilatations, which, therefore, do not disappear.

Such a case occurred in the present series, and is illustrated.

The remaining 40 cases were then considered. Two of these were set apart as instances of "congenital cystic disease of the lung," (see section on pathogenesis), leaving 38 cases to be classified.

113. Sparks, J. V.: *Brit. J. Radiol.* 4:30, 1931.

These 38 cases were grouped according to the bronchographic changes, as has just been described. The final analysis of all 68 cases was, then, as follows:

Atelectatic bronchiectasis (1 case classified on morbid anatomic basis)	42 (61.8 per cent)
Bronchogenic (or bronchopneumonic) bronchiectasis.....	24 (35.2 per cent)
"Combined" forms	0
Congenital cystic disease.....	2 (3 per cent)

The high incidence of the atelectatic type will be noted.

This simple classification of bronchiectasis, apart from its general convenience, is likely to be of value chiefly as a guide to prognosis and treatment. The classification submitted here is capable of acting as a basis for that exclusive and detailed study of the prognosis of bronchiectasis as a whole which has not yet been made, but which is so urgently required.

As regards treatment, the decision for or against operation and as to the best time if operation seems advisable is of vital importance in each case. Many aspects of the case must be considered before the final decision is reached, but perhaps the most important of these is the prospect of cure or satisfactory improvement if nonsurgical measures are undertaken. It is in this connection that the present classification is likely to be helpful.

The occurrence of temporary bronchiectasis was referred to in the section on pathogenesis, and it will be remembered that only in cases of atelectasis was this temporary condition reported. Now, although in the majority of the atelectatic lobes in the present series the bronchi were found to be seriously damaged, there were several in which such damage was relatively slight. Furthermore, the average duration of disease in the 42 cases of atelectatic type, before diagnosis, was seven years and four months. This is less than half that in the cases of bronchogenic type, but is nevertheless considerable. With earlier diagnosis, it seems probable that the percentage of cases in which restoration to normal is possible would be greatly increased. In a case of atelectatic bronchiectasis of recent onset or in one in which infection is moderate, active nonsurgical treatment by adequate postural drainage, breathing exercises and the bronchoscopic method, if necessary, together with any other indicated measures, such as the removal of chronic sinusal infection, should be given full trial before surgical intervention is even considered. In a case of bronchogenic type, on the other hand, permanent success with medical treatment is much less likely, and the decision rests rather on the degree of bronchial infection, the general condition of the patient and the presence or absence of suppurative sinusitis. It is considered likely that in most of these cases operation will eventually be required if a cure is

desired and that this should not be postponed beyond the age of childhood unless bronchial infection is slight.

It is proposed to conclude this section with a brief general account of the two groups which were set up, the atelectatic and the bronchogenic. The etiologic factors in the two groups did not differ significantly, although bronchitis, primary and secondary, was much more frequent as a causal factor in the atelectatic group (29 against 16 per

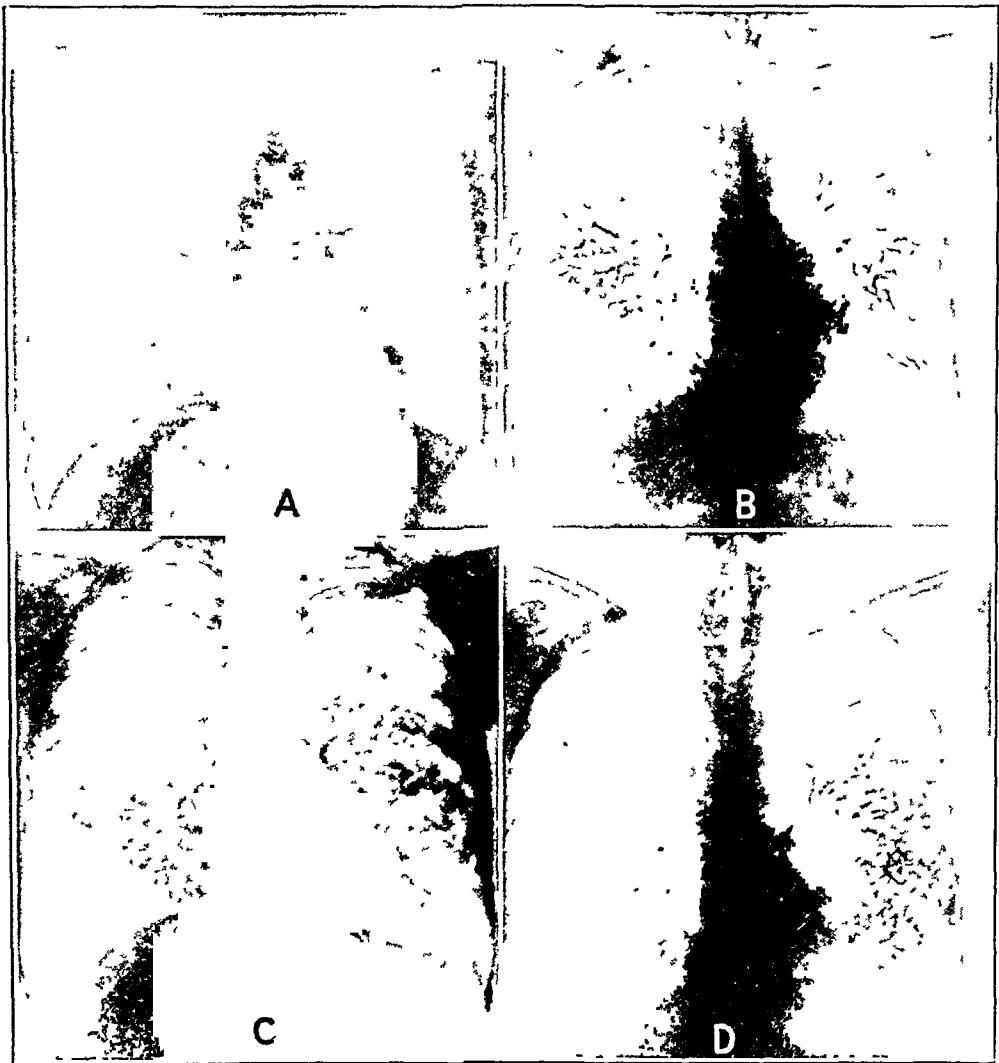


Fig. 23.—This case of atelectatic bronchiectasis was one in which disappearance of the triangular shadow was not accompanied by disappearance of the dilatations. *A*, original roentgenogram. Note the shadow at the base of the left lung. *B*, original bronchogram. Note the dilatations crowded within the triangular shadow. *C*, second roentgenogram. Note the absence of a triangular shadow. *D*, second bronchogram. Note the persistence of the bronchial dilatations and the slight change in their relative positions.

cent). No conclusion with regard to infection of the upper respiratory tract could be reached, owing to the small number of cases in which sinusitis was discovered. A "spontaneous" onset was equally common in the two groups (39 and 44 per cent). Clinically, a much higher incidence

of those recurrent febrile exacerbations which have been referred to as "chest attacks" was found in the atelectatic group (31 against 4.4 per cent). It seemed probable that this increase was due to recurrent "retention" bronchiolitis or so-called pneumonitis, which would more readily occur in a collapsed lobe. A much stricter localization of clinical signs was also noticed in cases of the atelectatic group. Physical signs were confined to the basal region near the spine in 38 out of 42 cases, and in 3 others in which axillary signs were present subsequent investigation revealed infection of the lingula or middle lobe of the right lung. It was true that this strict localization of signs did not always correspond with the extent of the disease, which was sometimes greater than the signs suggested. However, since this localization of physical signs was present in only 1 out of 24 cases of the bronchogenic type, it was a helpful differentiating point. In the other 21 cases of the bronchogenic form with adequate signs these were widespread over the base and in the lower part of the axilla, in spite of the fact that only one lobe was affected on either side in the great majority of instances. In 2 cases of bronchogenic type physical signs were slight or absent. Otherwise, the clinical manifestations in the two groups were almost identical, including clubbing of the digits (63 and 64 per cent). The general health was the same in the two groups.

The ordinary roentgenograms, however, showed some striking differences, although these were of doubtful value in differential diagnosis. "Fibrotic" shadows were more frequently met with in the bronchogenic group (50 against 78.3 per cent), and triangular shadows were found only in the atelectatic group. They were present in 40.5 per cent of cases, and "fibrotic" shadows were actually more frequently seen in cases of the atelectatic form than were the typical triangular shadows. This lends emphasis to the suggestion of Lander, which was discussed in the section on the roentgenologic features, that the criteria of collapse required extension, or at least reconsideration. It may be that the crowding and abnormal distribution of the bronchi, which were used as a criterion in this essay, will supply this need, at least in part.

A summary of the salient features of each of the two main groups, as noted in the present series, is given in the following tabulation.

Features	Comment
Etiologic	Bronchitis was nearly twice as common in the atelectatic group.
Clinical	Febrile "chest attacks" were seven times as frequent in the atelectatic group.
	Strict localization of physical signs was usual in cases of atelectatic bronchiectasis, but infrequent in those of the bronchogenic type.

Features	Comment
Roentgenographic	"Fibrotic" shadowing was much more commonly seen in the bronchogenic group. Triangular shadows were met with only in cases of the atelectatic type, but were seen in only 40 per cent of these.
Bronchographic	Crowding of affected bronchi was the rule in atelectatic bronchiectasis, though 1 exception was noted. Crowding of affected bronchi was not seen in a case of the bronchogenic type.

PROGNOSIS AND DEATH

Factors in Prognosis.—Any discussion of the prognosis of bronchiectasis almost inevitably recalls Laennec's famous patient,²⁵ an unmarried woman of 82. She steadily followed her occupation as *maitresse de piano*, although she had suffered from a persistent cough with purulent sputum since the age of 16. Laennec saw her a short time before her death, and at autopsy found a gross degree of bronchiectasis affecting all three lobes of the right lung and the upper lobe of the left lung!

Such cases of long standing, in which symptoms are compatible with fairly good health and ability to work normally, are commonly met with. On the other hand, all physicians are familiar with patients who succumb to one or another complication after a year or so.

This extreme variability in the outlook precludes any general estimate of prognosis, and a detailed study of an extensive series of groups of cases is now overdue.

What is required is information which will enable the physician to make a reasonable and reasoned estimate of the prospects in the individual case. The value of this is evident when the question of surgical intervention arises, as it now does in the majority of cases. The physician is naturally loath to advise an operation, which is still a serious risk to the patient, in a case in which good general health and a comparatively normal life are possible, unless he can feel confident that operation will greatly prolong life and permanently relieve or abolish symptoms.

Experience and "clinical instinct" are repeatedly set at naught by the vagaries of chronic bronchiectasis. The factors which affect the prognosis or the extent to which they do so is not known with any certainty.

Which patients are good surgical risks, and which are bad ones? Is fetid expectoration a bad prognostic sign? What is the significance, if any, of clubbing of the digits? Does the coexistence of suppurative sinusitis reduce the expectancy for life, and to what extent? Are there any other etiologic or clinical features which are of value in this respect? These are a few of the questions which await an answer.

The literature which was consulted did not greatly help to elucidate these problems, because general statements of mortality after an average period of observation give no guidance in the individual case.

In a recent article, Cookson and Mason¹¹⁴ were emphatic as to the risks to which the bronchiectatic patient is exposed if there is no surgical intervention. They reported a series of striking instances of sudden and fatal complications occurring in patients who were awaiting operation. They concluded that bronchiectasis is a fatal disease and that operation offers the main hope of cure or prolonged life.

Here, again, however, one is faced with the problem of the selection of the right case for operation, knowing, as one does, the possible duration of good health and general activity in some established cases. One of the patients in the present series is now well and free of cough and sputum after expectorating fetid material for fifty years, and Ballou, Singer and Graham¹³ stated that in some cases bronchiectasis may become dry! The analysis of the 68 cases which now follows cannot supply an answer to the problem, in view of the small number and the short period of observation (less than six years). It is submitted, however, as an indication of the *kind* of information which I believe is required. It may, in addition, have some suggestive value.

Analysis of Sixty-Eight Cases of Bronchiectasis from the Standpoint of Prognosis

Present Condition

Fifteen are known to be dead, 6 of whom died after operation.

Four are known to be in poor health, 2 of them after operation.

Twenty-five are known to be well and symptom free, 16 of them after operation.

Nineteen are known to be *in status quo*, 6 of them after operation.

The present condition of 5 is unknown.

Fetid Expectoration

	Total Number	Number Dead	Percentage Dead	Number Operated On	Postoperative Mortality, Percentage
Patients with fetid sputum.....	18	6	33.4	13	38.6
Patients without fetid sputum....	50	9	18	23	13.0

Clubbing of the Digits

	Total Number	Number Dead	Percentage Dead	Number Operated On	Postoperative Mortality, Percentage
Patients with clubbing.....	42	11	26.2	25	24.0
Patients without clubbing...	26	4	15.4	11	18.2

Atelectatic and Bronchogenic Groups

	Total Number	Number Dead	Percentage Dead	Number Operated On	Postoperative Mortality, Percentage
Atelectatic group.....	42	12	28.6	23	30.4
Bronchogenic group.....	24	3	12.5	13	7.7

Etiologic Factors Other Than Sinusitis

	Total Number	Number Dead	Percentage Dead
Pneumonia.....	23	8	34.8
Bronchitis.....	14	5	35.4
"Spontaneous" occurrence.....	29	2	7.1

114. Cookson, H. A., and Mason, G. A.: *Edinburgh M. J.* 45:844. 1938.

It was emphasized that these figures can have no more than suggestive value. Such as they are, however, they seem to indicate that fetid expectoration is an unfavorable prognostic sign, the mortality being almost double that among patients without fetid expectoration, and also that patients with this condition are less favorable operative risks. Clubbing of the digits seems a less valuable criterion, although the figures tend in the same direction.

Perhaps the most striking results are to be seen in the comparison of the two groups (the atelectatic and the bronchogenic). The mortality in the atelectatic group is more than twice, and the operative mortality nearly four times, that in the bronchogenic group. The operative risks must be balanced carefully against the prognosis for medical treatment in any study of the question.

Etiologically, the cases were classified into general groups in order to avoid absurdly small numbers. It is interesting to observe the low death rate in the group with "spontaneous" origin—only one-fifth that in the other groups.

It is not proposed to speculate on the causes of these apparent factors in prognosis. When statistically convincing information is at hand, it will be time enough for an investigation of the why and the wherefore.

It may be stated that the duration of symptoms did not appear to have any bearing on the prognosis. For the 15 patients who died, 8 of them after operation, the average duration was eleven and two-tenths years, exactly that for the whole 68 patients.

The factor of age must next be mentioned. It is particularly with reference to the results of operation that the question of age assumes importance. The average age of the 28 patients who survived operation was 15.6 years, and the average of the 8 who died soon after operation was 20.4 years. These averages were exactly the same as the corresponding figures for the whole series, but of the 13 children aged 12 and under at the time of operation only 1 died, whereas of the 23 patients aged 13 or over, 7 died after operation. These figures are small, but represent a mortality of 7.7 per cent, as against one of 30.8 per cent. Figures, however, do not illustrate the position adequately. The remarkably rapid and uneventful postoperative course of lobectomy in children is repeatedly observed and is in marked contrast to the prolonged, uncertain and anxious period of recovery in older persons. The only certainty with regard to operative prognosis at present is that the risk rises rapidly with age once childhood is left behind.

Although they may maintain a good standard of general health for many years, patients with bronchiectasis have a reduced resistance to infection and are unlikely to regain their health when once it has broken down. This fact was observed in patients whose cases were included in

the present series and is, I think, generally accepted. Of 9 patients who were in poor health when first seen, only 3 are now alive, and all of these are bedridden.

There is one other prognostic sign of certain value, and that is persistent albuminuria. Bronchiectatic patients with persistent albuminuria are not likely to live long and are likely to collapse if the slightest surgical intervention, even bronchoscopic examination, is attempted.¹¹⁵ It is generally held that persistent albuminuria, apart, of course, from complicating nephritis, is an indication of the development of amyloid disease.

Bronchiectasis which is secondary to fatal conditions, such as bronchial carcinoma or aortic aneurysm, has often no influence on the prognosis, but in some cases may hasten the end by the development of those complications which are more peculiar to itself and which are to be dealt with later in this section.

Fatal Complications.—Certain of the nonfatal complications have already been mentioned in the course of this essay. The course of the disease tends to undergo no dramatic changes until the final breakdown occurs. Febrile exacerbations, which were referred to under the name of "chest attacks," are liable to occur and to recur from time to time in certain cases. Sinusitis is frequent, but is usually symptomless.¹¹⁶

It is now necessary to refer to those more serious complications which herald, if they do not immediately bring about, a fatal termination of the disease.

These may be classified into three groups:

- A. Complications related to local exacerbation or to direct spread of infection within the lungs or thoracic cavity.
- B. Complications which are a direct result of associated conditions or intercurrent disease.
- C. Dissemination of infection by the blood stream and the late results of chronic sepsis.

A. *Intrathoracic Complications:* In certain cases of bronchiectasis a gradual increase in the symptoms, accompanied by an irregular, and probably a moderate, degree of fever, indicates an exacerbation of the disease. There is no acute onset, but a steady decline in the general health takes place, and although death does not occur for months, or perhaps a year or two, the general condition fails to improve and it is necessary to recognize that a limit to the life of the patient has been set. There were 7 cases in which the patients exhibited this gradual change in the general course of the disease. Five of the patients are now dead. The other 2 are still alive, but both are ill, febrile and emaciated.

115. Mason, G. A.: Personal communication to the author.

116. Walsh, T. W., and Meyer, O. O.: Coexistence of Bronchiectasis and Sinusitis, *Arch. Int. Med.* **61**:890 (June) 1938.

These 7 cases thus account for a third of the total deaths during the period of observation.

The cases in which there are febrile exacerbations, or "chest attacks," are readily differentiated from these cases of declining health. The onset is acute with high fever, the duration is short and the general health is rapidly regained. In fact, a child may be taken ill on Friday night and be at school on Monday. These acute attacks had no noticeable effect on the prognosis in the present series, and the case mortality was exactly the same as that for the whole series.

Acute fatal exacerbations do, however, frequently occur, whether as a terminal event in the type of case which has just been described, or as an abrupt complication in a case in which the patient has been previously well and active. They take the form either of local abscess or of gangrene, with or without resulting empyema or pyopneumothorax, or of aspiration pneumonia affecting a previously healthy lobe or lung. It is usually not possible to obtain evidence of any external infection as a determining factor in the occurrence of such a fatal complication, although one would think that this must be the cause in some cases.

In cases in which death occurs from postoperative infection, it is not uncommon to find suppurative pericarditis as the probable cause of death.¹¹⁷ No evidence of pericarditis was found, however, in patients who died of the disease itself, without operation, at the Royal Victoria Infirmary over a ten year period.

Finally, some patients who suffer from bronchiectasis die of cardiac disease (see also section C). Cookson and Mason described a case in which I had an opportunity of seeing the patient, a young man of 25. He had had symptoms of bronchiectasis for six years, during which time foul expectoration had been persistent. For the greater part of the year prior to admission to the hospital his health had been steadily declining, and he was ill on admission. Two days later he became very ill, with high temperature, and auricular flutter developed, which persisted until death, ten days later.

Another patient who died of cardiac failure, in the Royal Victoria Infirmary, had suffered from cough and expectoration for many years. Autopsy revealed that he had extensive bronchiectasis, with much parenchymal scarring. The right side of the heart was greatly dilated, and it seems possible that death was due to increased resistance in the pulmonary circulation, although it remains uncertain whether this is to be ascribed directly to the bronchopulmonary condition.

This case was taken from the pathologic records of the Royal Victoria Infirmary, and was not included in the present series. Both Moll⁶⁵ and Jex-Blake¹¹⁸ reported deaths from cardiac failure.

117. Mason, G. A.: Personal communication to the author.

118. Jex-Blake, A. J.: *Brit. M. J.* 1:591, 1920.

Finally, the occurrence of fatal hemoptysis, though not observed in the present series, was reported by several authors.¹¹⁹

B. Complications of Associated Conditions and Intercurrent Diseases: Bronchiectasis may be only an indirect cause of death, or the patient may die of intercurrent disease.

When bronchiectasis is due to carcinoma of the bronchus or to an aneurysm or is associated with tuberculosis, death is not infrequently due to the primary disease or its complications. No cases of such nature were included in the present series. In addition, associated sinusitis or otitis is not uncommon in cases of bronchiectasis, according to the literature, and it is likely that more instances of such association would

TABLE 1.—*Causes of Death in the 27 Cases of Bronchiectasis in Which Autopsy Was Performed at the Royal Victoria Infirmary, Newcastle-on-Tyne, 1929 to 1938*

A. Intrathoracic, direct	
Abscess and gangrene of the lung.....	7
Suppurative bronchopneumonia	7
Empyema (probably secondary to pulmonary abscess).....	2
Lobar pneumonia (?)	1
Cardiac failure	1
Total.....	18
B. Associated conditions and intercurrent disease	
Intracranial abscess *	5
Flare-up of existing tuberculosis.....	1
Pneumococcal peritonitis	1
Portal pyemia	1
Total.....	8
C. Infection of the blood stream and the late results of chronic sepsis	
General pyemia	1

* Intracranial abscess was placed in group B, in view of recent evidence against the idea that its causative agent is blood borne, but this does not mean that an attempt has been made to prejudge the question.

have been recognized among the 68 cases had a special search been instituted. The patient with such an associated sinusitis is liable to the complications of this condition, as well as those of his bronchiectasis. Adams,¹²⁰ for instance suggested that cerebral abscess, the classic fatal complication of bronchiectasis, may often be in reality a complication of sinusitis when this is present. Indeed, he expressed the opinion that both the bronchiectasis and the abscess may be directly due to sinusal infection.

The rarity of cerebral abscess in pyemic states, even when abscesses are present in the lung, was commented on by Ballou, Singer and Graham¹³ and by Goodman,¹⁶ and the frequency of cerebral abscess as a cause of death in cases of bronchiectasis seems to demand some

119. Jex-Blake.¹¹⁸ Moll.⁶⁵

120. Adams, J.: J. Laryng. & Otol. 40:172, 1925.

such explanation as was offered by Adams. Osler and McCrae ¹²¹ cited the 13,700 autopsies at the London Hospital and the Brompton Hospital which were reported by Schörstein. Among them were 19 instances of cerebral abscess associated with pulmonary disease, usually bronchiectasis.

In table 1, in which are listed cases of death from bronchiectasis at the Royal Victoria Infirmary in the ten years from 1929 to 1938, it will be noted that intracranial abscess was the cause in 5 out of 27 cases. This incidence of intracranial abscess compares with Tuffier's ¹²² report of 6 instances of intracranial abscess in 45 cases, Schörstein's estimate

TABLE 2.—*Causes of Death in 55 Cases of Fatal Bronchiectasis (Moll ⁶⁵)*

Bronchopneumonia.....	16
Empyema.....	10
Pyopneumothorax.....	3
Cardiac failure.....	4
Cerebral abscess.....	3
Gangrene of lung.....	2
Pulmonary abscess.....	1
Hemoptysis.....	1
Nephritis.....	1
Other causes.....	14

TABLE 3.—*Causes of Death in 110 Cases of Fatal Bronchiectasis (Jex-Blake ¹¹⁸)*

Bronchopneumonia.....	34
"Exhaustion".....	34
"Exhaustion" and asphyxia.....	8
Cerebral abscess.....	15
Cerebral new growth.....	2
Hemoptysis.....	5
Heart failure.....	3
Postoperative collapse.....	3
Intercurrent disease.....	3
Septic diarrhea.....	1
Lobar pneumonia.....	1
Influenzal pneumonia.....	1

of cerebral abscess as the cause of death in 20 per cent of cases and Moll's ⁶⁵ report of 3 cases of abscess of the brain in 55 cases of fatal bronchiectasis.

Finally, the death of patients suffering from bronchiectasis may be due to intercurrent disease which has no apparent connection with the bronchopulmonary condition. Only 2 examples of such death were noted in the pathologic records. One was that of a girl of 9, who died of pneumococcic peritonitis. The other occurred in a patient who died of portal pyemia, which could not be related to the bronchial disease. One

121. Osler, W., and McCrae, T.: *The Principles and Practice of Medicine*, ed. 9, New York, D. Appleton and Company, 1920, p. 617.

122. Tuffier: *Bull. et mém. Soc. de chir. de Paris* **36**:529, 1910.

patient died of acute lobar pneumonia, but his case was not included, as it was not considered possible to exclude the connection of this with preexisting bronchiectasis.

C. Infection of the Blood Stream and the Late Results of Chronic Sepsis: Only 1 apparent example of infection of the blood stream was noted in the pathologic series of 27 cases recorded at the Royal Victoria Infirmary. This was the case of a woman who died of general pyemia for which no cause apart from the bronchiectasis was to be found. This complication must be rare.

The only late results of chronic sepsis which appear to occur are amyloid disease and myocardial damage; and neither can be shown to be at all frequent as a direct cause of death. The significance of Jex-Blake's¹¹⁸ 34 cases of "exhaustion" is difficult to assess. No example of either amyloid disease or myocardial damage was noted as a cause of death in the present investigation, although it is difficult to exclude the 2 instances of death from cardiac disease, cited in section A. It may be that they should have been included here, although the balance of evidence was held to be in favor of regarding them as the result of true intrathoracic complications.

SUMMARY AND CONCLUSIONS

1. Sixty-eight cases of bronchiectasis which I observed over a period of several years are reported.

2. An account of the anatomy and physiology of the normal bronchi, based on a study of the recent literature and on a dissection of a normal bronchial tree, is presented.

3. An analysis of the records of the 68 cases, including a pathologic examination of lobes excised at operation in 28 cases, is made, and the relevant literature is reviewed.

4. The pathogenesis, the etiology and the clinical and roentgenologic features of the disease are described on the basis of this analysis.

5. A classification is suggested, which recognizes congenital cystic disease of the lung and atelectatic and bronchogenic types of acquired bronchiectasis.

6. Finally, the problem of prognosis of and the causes of death from bronchiectasis are discussed. This discussion is based on the results in the 68 cases, on the autopsy records of the Royal Victoria Infirmary from 1929 to 1938, inclusive, and on a study of the literature.

7. The conclusion is reached that bronchial dilatation may be temporary or permanent. Temporary bronchiectasis is always due to collapse of the lung tissue, but permanent bronchiectasis is the result

of the interaction of many factors, of which the most important is infection of the bronchial wall.

8. The numerous pathogenic factors in the evolution of bronchiectasis are grouped under two heads: (*a*) defects in the bronchial wall and (*b*) excessive strain and stress to which the bronchial wall may be subjected.

9. The question of "congenital bronchiectasis" is left open, as no conclusive evidence of its existence apart from congenital cystic disease of the lung has been found. The difficulties in the solution of the matter are discussed.

10. The value of an accurate history and of careful physical examination in the diagnosis of bronchiectasis is emphasized. In but few cases have physical signs been absent.

11. The need for a detailed and extensive study of the prognosis in selected groups of cases is emphasized. An analysis of the present series is made in order to illustrate the suggested type of investigation of prognosis.

12. The causes of death in bronchiectasis are classified into three groups: (*a*) local exacerbation or spread of infection within the lungs or thoracic cavity; (*b*) direct complications of associated conditions and intercurrent disease, and (*c*) dissemination of infection by the blood stream and the late results of chronic sepsis.

Dr. G. Hall and Dr. T. C. Hunter gave me permission to cite cases at one time under their care in the Royal Victoria Infirmary. Prof. A. F. Bernard Shaw gave me access to and permission to quote from the pathologic records of the Royal Victoria Infirmary. Dr. S. Whately Davidson, Hon. Radiologist to the Royal Victoria Infirmary and Radiologist to the Newcastle General Hospital gave me access to and permission to cite from and reproduce roentgenograms taken at these hospitals, under his supervision. Mr. George Mason, Surgeon in Charge, Department of Thoracic Surgery, Newcastle General Hospital, and Hon. Assistant Surgeon, Royal Victoria Infirmary, gave me access to cases, records and pathologic material under his charge, and permitted me to quote and reproduce certain operative records and pathologic specimens. Dr. G. A. Smart prepared the photomicrographs.

BLOOD PRESSURE STUDIES ON WEST INDIANS AND PANAMANIAN LIVING ON THE ISTHMUS OF PANAMA

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ANCON, CANAL ZONE

The purposes of this paper are (1) to compare the incidence of hypertension in West Indians and Panamanians living on the Isthmus of Panama, and (2) to provide data which may be of value in considering the relation between arterial tension and such factors as race, heredity and climate.

LITERATURE

Reports on the blood pressure of various peoples and on the importance of race and climate as factors influencing blood pressure have not been numerous, and the results are inconclusive.

Philippines.—Musgrave and Sison¹ expressed the belief that blood pressure in persons living in the tropics is low. The average systolic blood pressure for 30 native males was 108 mm. of mercury and for 19 females 113 mm. Figures given for foreigners included 124 mm. after one year of residence, 115 mm. after one to five years of residence and 113 mm. after ten years of residence. Chamberlain² stated that the average systolic blood pressure of American soldiers stationed in the Philippines was 115 mm. for ages 18 to 30 and 118 mm. for ages 30 to 40. Filipinos had almost identical blood pressures. He claimed that, except for a slight fall during the first three months, there was no tendency for the blood pressure to drop with increasing time of residence in the Philippines. Concepción and Bulatao³ reported similar findings but drew different conclusions. The average blood pressure of 717 males with an average age of 28.5 years was 115 mm. systolic and 79 mm. diastolic and for females 116 mm. systolic and 83 mm. diastolic. They concluded that the blood pressures of Filipinos were lower than those of Americans living in the United States but the same as those of Americans

From the Board of Health Laboratory, Gorgas Hospital.

1. Musgrave, W. E., and Sison, A. G.: Blood Pressure in the Tropics, *Philippine J. Sc. B* 5:325, 1910.

2. Chamberlain, W. P.: A Study of Systolic Blood Pressure and Pulse Rate of Healthy Adult Males in the Philippines, *Philippine J. Sc. B* 6:467, 1911.

3. Concepción, I., and Bulatao, E.: Blood Pressure of Filipinos, *Philippine J. Sc. B* 11:135, 1916.

living in the Philippines. Siler ⁴ observed: "Blood pressures in the general run of individuals living in tropical countries are maintained at lower levels than in temperate or colder climates."

China.—Cadbury ⁵ wrote: "Hypertension as a pathological condition is rare in China." The average systolic blood pressure of Cantonese students was 20 to 30 mm. less and the average diastolic blood pressure 10 to 20 mm. less than those of Europeans and North Americans. Kilborn ⁶ reported that blood pressures of persons living in China tended to be low. Tung ⁷ revealed that the average blood pressure of Americans dropped from 118 mm. systolic and 76 mm. diastolic to 109 mm. systolic and 65 mm. diastolic after three years' residence in Peiping. Foster ⁸ stated: "The blood pressure of the Chinese is lower than the general average for western countries. Foreigners living in China tend to develop lower blood pressures." Of 4,000 Chinese patients in the Hunan-Yale Hospital only 20 were found to have a blood pressure over 160 mm. Twenty-two of 33 Americans showed a fall of blood pressure after residence in China.

Japan.—Tanemura ⁹ reported that the average blood pressure of males aged 19 was 122 mm. systolic and 83 mm. diastolic.

Egypt.—Ismail ¹⁰ claimed that 10 per cent of all his private patients had essential hypertension.

India.—McCay, ¹¹ using the palpatory method on 500 male Bengalis aged 20 to 25, found that the systolic blood pressure was 90 to 105 mm., while the range for Europeans in Calcutta was 115 to 130 mm.

Australia.—Nye ¹² denied the presence of hypertension in the Australian aborigines.

4. Siler, J. F.: Annual Physical Examinations of Officers in the Philippine Islands, Mil. Surgeon **56**:738, 1925.

5. Cadbury, W. W.: The Blood Pressure of Normal Cantonese Students, Arch. Int. Med. **30**:362 (Sept.) 1922.

6. Kilborn, L. G.: Blood Pressure of Szuchaenese Students, China M. J. **40**: 1, 1926.

7. Tung, C. L.: Relative Hypotension of Foreigners in China, Arch. Int. Med. **40**:153 (Aug.) 1927.

8. Foster, J. H.: Blood Pressure of Foreigners in China, Arch. Int. Med. **40**: 38 (July) 1927; Practice of Medicine in China and New England with Observations on Hypertension, New England J. Med. **203**:1073, 1930.

9. Tanemura, I.: Kyoto J. M. Sc. **15**:84, 1918; cited by Cadbury.⁵

10. Ismail, Abd-El-Aziz: Etiology of Hyperpiesis in Egyptians, Lancet **2**: 275, 1928.

11. McCay, D.: Lancet **1**:1483, 1907, cited by Cadbury; ⁵ Scientific Memoirs of Government of India, 1908, no. 34, p. 23; cited by Cadbury.⁵

12. Nye, L. J. J.: Blood Pressure in the Australian Aboriginal with Consideration of Possible Aetiological Factors in Hyperpiesia and Its Relation to Civilization, M. J. Australia **2**:1000, 1937.

Africa.—Donnison¹³ reported that the blood pressures of Negroes living under primitive native conditions were similar to those of white persons up to the age of 40. After 40 the blood pressure of white persons increased, while those of Negroes declined.

United States.—Alvarez and Stanley¹⁴ noted that older Mexican prisoners rarely showed an increase in blood pressure. The tension of Negro prisoners was higher than normal. Allen¹⁵ found that 55.6 per cent of 1,000 Negro factory workers in Cleveland and 33.5 per cent of 2,000 white workers had cardiovascular abnormalities. Hypertension constituted 45 per cent of the cardiovascular abnormalities. Adams¹⁶ recorded slightly higher average blood pressures for Negro workmen than for white workmen in New Orleans. Lemann¹⁷ was unable to find remissions of high blood pressures in 45 patients during a long, continued, subtropical summer in New Orleans. Flaxman¹⁸ found that hypertension was more common among Negroes than among white persons in the Middle West and that they died of heart disease earlier. Schultze and Schwab¹⁹ noted that there was a greater incidence of hypertension in Southern Negroes than in white persons.

Arctic Region.—Firestone²⁰ found that Eskimos had the same incidence of hypertension as was reported for inhabitants of the United States.

West Indies.—Roddiss and Cooper²¹ observed that the average systolic blood pressure of 67 officers of the United States Navy on temporary duty in the West Indies was 11.4 mm. less than the average for a similar group of men living in the United States. They noted a gradual rise in the blood pressures of 16 officers on return to colder climates.

13. Donnison, C. P.: Blood Pressure in African Natives, *Lancet* **1**:6, 1929.

14. Alvarez, W. C., and Stanley, L. L.: Blood Pressures in Six Thousand Prisoners and Four Hundred Prison Guards, *Arch. Int. Med.* **46**:17 (July) 1930.

15. Allen, F. P.: Cardio-Vascular Impairment Among One Thousand Negro Factory Workers, *J. Indust. Hyg.* **13**:164, 1931.

16. Adams, J. M.: Some Racial Differences in Blood Pressures and Morbidity in a Group of White and Colored Workmen, *Am. J. M. Sc.* **184**:342, 1932.

17. Lemann, I. I.: Effect of a Long Continued Subtropical Summer on High Blood Pressure, *Am. J. Trop. Med.* **12**:331, 1932.

18. Flaxman, N.: Heart Disease in the Middle West, *Am. J. M. Sc.* **188**:639, 1934.

19. Schultze, V. E., and Schwab, E. H.: Arteriolar Hypertension in American Negroes, *Am. Heart J.* **11**:66, 1936.

20. Firestone, cited by Blackford, J. M.; Bowers, J. M., and Baker, J. W.: Follow-Up Study of Hypertension, *J. A. M. A.* **94**:328 (Feb. 1) 1930.

21. Roddiss, L. H., and Cooper, G. W.: The Effect of Climate on Blood Pressure, *J. A. M. A.* **87**:2053 (Dec. 18) 1926.

Panama.—Thonnard-Neumann²² recorded a systolic blood pressure of over 140 mm. in 33.5 per cent of 500 West Indians living in Panama. The average age was 40.

STUDY I

Col. Robert M. Hardaway, chief of the medical service of Gorgas Hospital, was impressed by the difference in the incidence of hypertension between West Indians and Panamanians.²³ An opportunity to analyze phases of this difference presented itself when, after years of simple operation and maintenance, the government embarked on an extensive building program for the Panama Canal. Within a few months, several thousand candidates for employment were given a complete physical examination.

Method.—1. The statistics were gathered on 1,328 consecutive male candidates for employment on the Silver Roll of the Panama Canal between October 1939 and April 1940. (The Silver Roll employs unskilled or slightly skilled laborers, generally Panamanians and West Indians, whereas the Gold Roll employs, for the most part, skilled Americans.)

2. The readings were taken under identical conditions for the two race groups by one observer, who examined 25 to 35 men daily.

3. One new mercury sphygmomanometer, which had been checked for accuracy by the United States Bureau of Standards, was used.

4. On completion of a routine physical examination, the candidates were permitted to rest for fifteen to thirty minutes. Readings were then taken on each seated candidate at three minute intervals until two consecutive systolic readings were within 6 mm. of mercury of each other. In a few cases this technic was only approximated.

22. Thonnard-Neumann, E.: Blood Pressure Studies in the West Indian Negroes, 18th Annual Report, Medical Department, United Fruit Company, Boston, 1929, p. 251.

23. Three fairly distinct race groups live on the Isthmus of Panama: Panamanians, West Indians and Americans.

By appearance, background, customs and language, these groups are easily separated. Of course, none of these groups meets the anthropologist's definition of "race." In this paper the term "race" is used colloquially, with appreciation of its scientific limitations.

The original Panamanian was an Indian. To his stock, for 300 years, has been added the blood of Europeans, Negroes, Chinese, etc. Today the Panamanian, especially of the cities, is a "Latin American."

When the Panama Canal was built, thousands of Negroes from Jamaica, the Barbados and other West Indian islands were imported as laborers. The ancestors of these Negroes had mixed to an indeterminate degree with many peoples since their transfer from Africa. Nevertheless, in Panama these Negroes and their families constitute a fairly definite group.

TABLE 1.—*Results of Study I*

Panamanians (P.) or West Indians (W. I.)	Age 16 to 25		Age 26 to 35		Age 36 to 45		Age 46 to 65		Total	
	P.	W. I.	P.	W. I.	P.	W. I.	P.	W. I.	P.	W. I.
Number of candidates	393	312	276	113	64	54	54	62	787	541
Percentage of race total.....	49.9	57.7	35.1	20.9	8.1	10.0	6.9	11.5	100	100
Average age, year	21.2	20.6	29.1	29.5	39.1	41.2	49.6	51.6	27.1	28.1
Average systolic blood pressure.....	104.9	114.5	106.6	117.8	102.9	127.2	115.0	135.8	105.6	119.0
Average diastolic blood pressure.....	72.2	78.1	73.9	83.0	76.3	88.8	76.9	91.6	74.9	81.7
Number with systolic blood pressure of 150 and over.....	1	13	2	8	2	11	5	21	10	53
Percentage with systolic blood pressure of 150 and over.....	0.3	4.2	0.7	7.1	3.1	20.4	9.3	33.9	1.3	9.8
Number with systolic blood pressure of 170 and over.....	0	6	1	4	1	4	1	13	3	27
Percentage with systolic blood pressure of 170 and over.....	0	1.9	0.4	3.5	1.6	7.4	1.9	21.0	0.4	5.0
Number with diastolic blood pressure of 100 and over.....	2	8	6	12	2	14	3	19	13	53
Percentage with diastolic blood pressure of 100 and over.....	0.5	2.6	2.2	10.6	3.1	25.9	5.6	30.6	1.7	9.8
Number with diastolic blood pressure of 120 and over.....	0	2	1	2	1	4	0	6	2	14
Percentage with diastolic blood pressure of 120 and over.....	0	0.6	0.4	1.8	1.6	7.4	0	9.7	0.3	2.6
Number with systolic blood pressure of 100 and under.....	172	77	99	23	26	7	11	7	308	114
Percentage with systolic blood pressure of 100 and under.....	43.8	24.7	35.9	20.4	40.6	13.0	20.4	11.3	39.1	21.1
Number with systolic blood pressure of 80 and under.....	19	9	10	1	7	1	1	3	46	14
Percentage with systolic blood pressure of 80 and under.....	4.8	2.9	6.9	0.9	10.9	1.9	1.9	4.8	5.8	2.6
Number with diastolic blood pressure of 60 and under.....	43	17	38	0	6	1	5	2	92	23
Percentage with diastolic blood pressure of 60 and under.....	10.9	5.4	13.8	0	9.4	1.9	9.3	3.2	11.7	3.7

5. Systolic blood pressure was read at the sudden appearance of a clear sound as the mercury column fell (beginning of first phase). Diastolic blood pressure was read at the initial replacement of the clear sounds by a muffled sound (fourth phase).

Definitions.—1. A “Panamanian” is one born in Panama whose parents were both born in Panama.

2. A “West Indian” is a Negro who was either born in the West Indies of West Indian parentage or whose parents both were born in the West Indies.

3. “Average blood pressure” of a person consists of the average of all the readings taken on that person. (A total of 3,388 readings were taken on 1,328 candidates, for an average of 2.6 readings for each person.)

Results.—These are summarized in table 1.

Comment.—1. The incidence of hypertension was much greater in West Indians than in Panamanians in each age group. Ratios were 16:1 for ages 16 to 25, 10:1 for ages 26 to 35, 7:1 for ages 36 to 45, 4:1 for ages 46 to 65 and 7:1 for the entire group.

2. The incidence of hypotension was much greater in Panamanians than in West Indians.

3. The age distribution of the candidates in each race group was almost identical.

4. The average blood pressures should not be given great significance because these averages include those of subjects with hypertension.

STUDY II

Since all the blood pressure readings in study I were taken by one observer, confirmatory evidence for the appreciable difference in the incidence of hypertension between West Indians and Panamanians was sought.

Method.—1. The records of 7 physicians doing the physical examinations were analyzed.

2. These physicians examined 40 to 100 men daily under conditions that were not especially adapted for blood pressure studies.

3. Several sphygmomanometers were used.

4. No attempts were made to standardize the time and technic of taking the blood pressures.

5. Only one reading was generally taken. When the initial reading was high and further observations were made, that reading which the individual examiner considered as final was utilized.

6. The same definitions of "Panamanian" and "West Indian" used in study I prevailed.

Results.—These are summarized in table 2.

Comment.—The records of the 7 physicians corroborate the findings in study I. The higher incidence of hypertension in both groups can be explained by the fact that in study II the blood pressure readings were taken under uncontrolled conditions, in which excitement may have been an important factor. Sufficient readings were not taken to eliminate that possibility. The ages were not studied because the results of study I indicated that the age distributions of the candidates of the two race groups were almost identical.

TABLE 2.—*Results of Study II*

Race Group	Total Number of Candidates	Number with Systolic Blood Pressure of 150 and Over	Percentage with Systolic Blood Pressure of 150 and Over
Panamanians.....	2,457	158	6.4
West Indians.....	745	175	23.5

TABLE 3.—*Results of Study III*

Race Group	Total Number of Women	Number with Systolic Blood Pressure of 150 and Over	Percentage with Systolic Blood Pressure of 150 and Over
Panamanians.....	410	12	2.9
West Indians.....	1,301	139	10.7

STUDY III

An entirely different group of persons was sought for further confirmation of the results of study I. Dr. Howard K. Tuttle permitted the use of the records of his large antepartum clinic.

Method.—1. The antepartum records from 1936 to 1940 were analyzed.

2. Only those cases were considered in which two or more readings of blood pressure were available.

3. The blood pressure reading at the initial visit was disregarded because the patient usually was excited on that visit.

4. Those subjects for whom a single reading on any of the visits, except the first, was 150 mm. or over were considered in the hypertensive group.

5. It was impossible to question the patients as to their birthplace, parents, etc., as was done in the first two studies. The distinction between Panamanian and West Indian was made on the basis of name alone; that is, when the name was "Spanish" the patient was considered Panamanian and when the name was "British" the patient was considered West Indian. Doubtful cases were disregarded. The person who "decided" the nationality of the patients has lived on the Isthmus for over twenty years and has had much experience with hospital patients. Records of the blood pressure were concealed until the decision was made, to avoid unintentional prejudice.

Results.—These are summarized in table 3.

Comment.—Although the possibility of error in distinguishing between Panamanian and West Indian has been introduced, it is believed that the error cannot be of significance.

TABLE 4.—*Summary of Answers to Questionnaires*

Questionnaires sent	110
Replies received	68
Opinion that incidence of hypertension is higher in West Indians	45
Opinion that incidence of hypertension is higher in Panamanians	2
Members unqualified or unwilling to give impression.....	21

STUDY IV

Method.—1. A questionnaire was sent to all members of the Medical Association of the Isthmian Canal Zone requesting their impressions as to the relative incidence of hypertension in West Indians and Panamanians.

Results.—The answers to the questionnaire are summarized in table 4.

COMMENT

The results of the four studies are in harmony and indicate that (*a*) the incidence of high blood pressure is much greater in West Indians than in Panamanians, and that (*b*) the incidence of low blood pressure is much greater in Panamanians than in West Indians.

The standards used in determining the presence of hypertension were high. A systolic blood pressure of 150 mm. is certainly abnormal under conditions of rest. If 140 mm. had been used the incidence of hypertension would have been higher in both groups, but the ratios would not have been altered.

Reaction of the West Indians and their descendants to a strange environment might have been responsible for the hypertension. How-

ever, reports from Phillips²⁴ indicate that the Negroes in Jamaica have a high incidence of hypertension.

The high incidence of hypotension in Panamanians, as is demonstrated in table 1, seems to substantiate in part the views of Robinson and Brucer²⁵ that levels of normal blood pressure must be revised downward. The evidence that hypotension is a disease or an important sign of one, except in such rare conditions as Addison's disease, has never been convincing. The possibility that tuberculosis or anemia may be responsible for hypotension in Panamanians exists, but it is my impression that hypotension is normal tension in Panama and elsewhere.

A high incidence of hypertension may be present among persons living in a tropical country.

The influence of heredity as a factor in hypertension is receiving increased consideration. Fishberg²⁶ stated: "In at least a large majority of instances essential hypertension arises on the basis of an inherited constitutional predisposition." The work of Hines²⁷ also indicated the importance of heredity in the problem of hypertension.

It should be understood distinctly that no attempt is being made to attribute the difference in arterial tension between West Indians and Panamanians to the difference in race. Neither group is a true race. Studies on the psychology, occupations, diet, habitus, anatomy and diseases of both peoples must be made before the etiologic factors for the differences will be apparent.

SUMMARY

1. Nine and eight-tenths per cent of 541 male West Indians living in Panama had an average systolic blood pressure of 150 mm. or over when the studies were made under controlled conditions. One and three-tenths per cent of 787 Panamanians tested under the same conditions had a systolic blood pressure of 150 mm. or over.

2. Twice as many Panamanians as West Indians had low blood pressures.

3. The average blood pressure of male candidates for employment, with ages ranging from 16 to 65, was 119 mm. systolic and 82 mm. diastolic, for West Indians, and 106 mm. systolic and 75 mm. diastolic, for Panamanians.

24. Phillips, C. B.: Reports to the Chief Health Officer, Canal Zone, 1940, unpublished data.

25. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure, *Arch Int. Med.* **64**:409 (Sept.) 1939.

26. Fishberg, A. M.: *Hypertension and Nephritis*, ed. 2, Philadelphia, Lea & Febiger, 1939, p. 613.

27. Hines, E. A., Jr.: The Heredity Factor and Subsequent Development of Hypertension, *Proc. Staff Meet., Mayo Clin.* **15**:145, 1940.

4. Twenty-three and five-tenths per cent of 745 other West Indians had a systolic blood pressure of 150 mm. or over when the readings were taken under uncontrolled conditions. Six and three-tenths per cent of 2,457 other Panamanians had a systolic blood pressure of 150 mm. or over under the same conditions.

5. Ten and seven-tenths per cent of 1,301 pregnant West Indian women had a single systolic blood pressure reading of 150 mm. or over while attending an antepartum clinic. Two and nine-tenths per cent of 410 Panamanian women had such a reading under like conditions.

6. Forty-five physicians of the Medical Association of the Isthmian Canal Zone thought West Indians have a higher incidence of hypertension than Panamanians. Two physicians thought that the incidence is higher in Panamanians.

Brig. Gen. Morrison C. Stayer, Chief Health Officer, Canal Zone, provided facilities for this work.

TRANSMISSION OF ANTIANEMIC PRINCIPLE ACROSS THE PLACENTA AND ITS INFLUENCE ON EMBRYONIC ERYTHROPOIESIS

I. QUANTITATIVE EFFECT OF DIETS CONTAINING VENTRICULIN

OLIVER P. JONES, PH.D.

BUFFALO

Studies of anemia in pregnancy¹ have directed attention to the hypothesis that the mother may not always have an adequate supply of blood-building material for both fetal and maternal demands and that the fetus may deplete the maternal stores regardless of the result to the mother.² More specifically, Wintrobe and Shumacker³ suggested that a macrocytic anemia might develop during pregnancy if the fetus derived its supply of antianemic principle from the mother to the extent that a deficiency was caused to exist in the storage of maternal liver factor. If this assumption is correct, one should be able to influence embryonic and fetal erythropoiesis by supplying the mother with a superabundance of antianemic principle. Although Wintrobe and associates⁴ were unable to influence the red cell count and the mean corpuscular volume of 21 and 23 day rabbit fetuses, they expressed the belief that this did not contradict their hypothesis because they assumed the addition of more antianemic principle to a fetus already supplied with a maximal quantity from the mother could not be expected to produce any significant effect. On the basis of the morphologic similarity between fetal blood and that

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The material in this paper was presented in part at the meetings of the American Association of Anatomists in Boston in 1939 and in Louisville, Ky., in 1940.

1. Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy: II. The Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation During Pregnancy, *Am. J. M. Sc.* **184**:663 (Nov.) 1932.

2. Strauss, M. B., and McDonald, W. J.: Polyneuritis of Pregnancy a Dietary Deficiency Disorder, *J. A. M. A.* **100**:1320 (April 29) 1933.

3. Wintrobe, M. M., and Shumacker, H. B.: Comparison of Hematopoiesis in the Fetus and During Recovery from Pernicious Anemia, Together with a Consideration of the Relationship of Fetal Hematopoiesis to Macrocytic Anemia of Pregnancy and Anemia in Infants, *J. Clin. Investigation* **14**:837 (Nov.) 1935.

4. Wintrobe, M. M.; Kinsey, R. E.; Blount, R. C., and Trager, W.: Studies of Blood Formation in the Fetus and Newborn: III. The Relationship of Anti-Anemic Principle, Assay of Fetal Liver and Placental Extracts in Cases of Pernicious Anemia and in Mosquito Larvae, *Am. J. M. Sc.* **193**:449 (April) 1937.

taken during relapse from patients with pernicious anemia, Wintrobe and Shumacker³ concluded that the blood of the newborn infant or of the fetus in the terminal stages of development is similar to that in patients with pernicious anemia during various phases of therapeutically induced remission. Chiefly because of these quantitative similarities, Stasney and Higgins⁵ selected the newborn rat as a suitable animal in which to study the effect of concentrated gastric juice administered intraperitoneally to the mother during the latter part of pregnancy. Both normal human and hog gastric juices produced significant changes in the red corpuscles of the newborn rat.⁶ Later Higgins and his students⁷ also reported that human gastric juice (administered orally), reticulogen (a liver extract with vitamin B₁, administered parenterally), extralin (a liver-stomach concentrate) and ventriculin (a desiccated preparation of hog stomach) administered during gestation accelerated fetal erythropoiesis. More recently Stasney and Burns⁸ have reported significant changes in the blood of opossum pouch young following the administration of concentrated normal gastric juice and concentrated solution of

5. Stasney, J., and Higgins, G. M.: The Effect of Normal Human Gastric Juice Administered to the Mother on the Size and Volume of the Erythrocytes of the Fetus, Proc. Staff Meet., Mayo Clin. **12**:490 (Aug. 4) 1937.

6. (a) Stasney and Higgins.⁵ (b) Stasney, J.; Higgins, G. M., and Mann, F. C.: The Size, Volume and Number of Erythrocytes of the Newborn Rat: Effect of Administration, to the Mother, of Gastric Juice of a Normal Hog, Proc. Staff Meet., Mayo Clin. **12**:699 (Nov. 3) 1937; (c) The Effect on the Developing Red Blood Cells in the Fetus of Administering Human and Hog Gastric Juice to the Adult Rat During Pregnancy, Am. J. M. Sc. **197**:690 (May) 1939.

7. (a) Briese, E., and Higgins, G. M.: The Effect of Feeding Ventriculin to Pregnant Rats, with Special Reference to the Size of the Red Blood Cells of the Young, Anat. Rec. **73**:105 (Jan.) 1939. (b) Higgins, G. M.: Personal communication to the author, regarding effect of extralin and reticulogen. (c) Schlicke, C. P.: The Effect of Normal and Abnormal Human Gastric Juice, Administered to the Mother, on the Blood of Newborn Rats: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:145 (March 8) 1939; (d) The Blood of Newborn Rats After Oral Administration to the Mother of Normal and Abnormal Human Gastric Juice, Am. J. M. Sc. **200**:155 (Aug.) 1940.

8. Stasney, J., and Burns, E. L.: Influence of Anti-Anemic Principles upon Size of Erythrocytes of Opossums (*Didelphis virginiana*) in Maternal Pouch, Proc. Soc. Exper. Biol. & Med. **42**:544 (Nov.) 1939; The Influence of Active and Inactive Anti-Anemic Principles upon the Size of the Erythrocytes of Opossums (*Didelphis virginiana*) in the Maternal Pouch, Am. J. Path. **17**:466 (May) 1941. Recently, Hays and Last (The Action of Liver Extract on the Size of Erythrocytes of the Opossum Embryo, J. Biol. Chem. **140**:lv [July] 1941) reported that they were unable to verify these experiments. It is difficult to evaluate the work on cell diameters by Stasney and Burns, since they measured only the largest cells in a given blood smear. Such a procedure introduces too much of the personal factor.

liver extract. Wigodsky and Ivy⁹ have been unable to confirm these results in rats. This may be due to the differences in the technic of measuring the cells, and according to a recent review by Schalm¹⁰ the method employed by Higgins and associates is the more accurate one. Bruner¹¹ has also reported similar negative results after injecting liver extract into pregnant rats as well as into young rats 4 to 24 days old. These negative results have been interpreted by Wigodsky and Ivy⁹ to substantiate Wintrobe and Shumacker's assumption³ that the addition of more antianemic principle to a system already adequately supplied should have no influence on the red cell picture of these animals.¹² Undoubtedly both Wintrobe and Ivy and their associates have overlooked the prehepatic, or primitive, generation of red cells in the embryo. These cells *proliferate, elaborate pigment and commence to mature before the liver is morphologically differentiated*. It must be remembered, however, that functional differentiation cannot be determined by the anatomic condition of an organ¹³ and may even appear earlier than anticipated.¹⁴ Regardless of whether antianemic principle is present in the various fetal livers as reported,¹⁵ or is absent,⁴ the primitive erythroblasts of the embryonic prehepatic period which are different from both definitive

9. Wigodsky, H. S., and Ivy, A. C.: Effect of Liver Extract, Injected Parenterally into Pregnant Mother, on Erythrocytes of Newborn Rats, *Proc. Soc. Exper. Biol. & Med.* **38**:787 (June) 1938. Noble, T. A.; Wigodsky, H. S., and Ivy, A. C.: Effect of Gastric Juice on Erythrocytes of Newborn Rats, *ibid.* **45**:373 (Oct.) 1940.

10. Schalm, L.: The Determination of the Mean Red Blood Cell Diameter and Its Clinical Value, *Folia haemat.* **63**:34, 1939.

11. Bruner, H. D.: Effect of Parenteral Liver Extract on the Blood Picture of New Born Rats, *Proc. Soc. Exper. Biol. & Med.* **41**:260 (May) 1939.

12. Fitz-Hugh, Creskoff and Taylor attempted to stimulate reticulocyte maturation by injecting liver extract parenterally into 9 individual rat fetuses in utero, but no significant change from the normal reticulocyte curve was obtained (*J. Clin. Investigation* **15**:468 [July] 1936).

13. Meulengracht, E.: Histologic Investigation into the Pyloric Gland Organ in Pernicious Anemia, *Am. J. M. Sc.* **197**:201 (Feb.) 1939.

14. Dalton, A. J.: The Functional Differentiation of the Hepatic Cells of the Chick Embryo, *Anat. Rec.* **68**:393 (July) 1937. Heuser, C. H.: The Early Establishment of the Intestinal Nutrition in the Opossum: The Digestive System Just Before and Soon After Birth, *Am. J. Anat.* **28**:341 (Nov.) 1921.

15. Berglund, H.; Watkins, C. H., and Johnson, R.: Rapid Stimulation of Hemoglobin Synthesis in Secondary Anemias After Feeding Fetal Calf's Liver, *Proc. Soc. Exper. Biol. & Med.* **25**:814 (June) 1928. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Rôle of the Liver in Hematopoiesis, *Am. J. M. Sc.* **188**:193 (Aug.) 1934. Wigodsky, H. S.; Richter, O., and Ivy, A. C.: The Presence of the Antipernicious Anemia Factor in an Extract of Fetal Bovine Livers, *ibid.* **197**:750 (June) 1939. Sharp, E. A.: Personal communication to the author.

erythroblasts and megaloblasts¹⁶ occurring in pernicious anemia do differentiate and mature at a slow rate. The differentiation of these primitive erythroblasts in tissue culture¹⁷ might be interpreted to indicate that it occurs in the absence of an erythrocyte-maturing principle or that the latter was present only in minute quantities.

The primitive red cells of the prehepatic period are formed intravascularly in the yolk sac and have been called megaloblasts by some authors,¹⁸ although the term primitive erythroblast first suggested by Maximow is a more appropriate one. According to Bloom¹⁹ and Kirschbaum,²⁰ definitive erythroblasts, or cells of the normoblastic series, are not formed in the rat yolk sac. Thus far my studies of the 11 day rat embryonic yolk sac have substantiated these claims. The primitive erythroblasts of the rat yolk sac have been described by Kirschbaum²⁰ as similar to the megaloblasts occurring in pernicious anemia but not identical with them. He expressed the belief that the differences in nuclear structure of these two hemoglobiniferous cell types cannot be explained on the basis of species variability alone.²¹ The nuclear pattern of the primitive erythroblast becomes coarser earlier and is more "normoblastic" than the chromatin pattern of genuine megaloblasts (plate III, Jones^{16b}). The embryonic primitive erythroblasts are further dis-

16. (a) Jones, O. P.: The Origin and Structure of Erythroblasts with Special Reference to the Megaloblast, Thesis, University of Minnesota, Graduate School, 1935; (b) Cytology of Pathologic Marrow Cells, with Special Reference to Bone Marrow Biopsies, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2043; (c) Nature of the Reticulocytosis in Pernicious Anemia Following Liver Therapy, Proc. Soc. Exper. Biol. & Med. **38**:222 (March) 1938; (d) Transmission of Antianemic Principle Across the Placenta and Its Effect on the Primitive Erythroblasts of the Eleven-Day Rat Embryo, Anat. Rec. **73** (supp. 3):29 (March 25) 1939; (e) Further Studies of the Transmission of Antianemic Principle Across the Placenta and Its Effect on the Primitive Erythroblasts of the Eleven-Day Rat Embryo, *ibid.* **76** (supp. 2):34 (Feb.) 1940. (f) Kirschbaum, A.: Blood Cell Formation in Mammalian Embryos from the First Appearance of Vascular Cellular Elements Through the Period of Hepatic Hemopoiesis, Thesis, University of Minnesota, Graduate School, 1936; (g) Cytological Studies of Mammalian Embryonic Blood Cells, Proc. Soc. Exper. Biol. & Med. **35**:542 (Jan.) 1937.

17. Bloom, W.: Cellular Differentiation and Tissue Culture, *Physiol. Rev.* **17**:589 (Oct.) 1937. Maximow, A.: Tissue Cultures of Young Mammalian Embryos, *Contrib. Embryol.* (no. 80) **16**:47, 1925.

18. Sabin, F. R.: Studies on Blood: The Vitrally Stainable Granules as a Specific Criterion for Erythroblasts and the Differentiation of the Three Strains of the White Blood-Cells as Seen in the Living Chick's Yolk-Sac, *Bull. Johns Hopkins Hosp.* **32**:314 (Oct.) 1921.

19. Bloom, W.: Embryogenesis of Mammalian Blood, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 863.

20. Kirschbaum (footnotes 16 f and g).

21. Jones,^{16b} p. 2060. Kirschbaum (footnotes 16 f and g).

tinguished from the pathologic megaloblasts by their inability to enucleate rapidly and the relatively infrequent occurrence of karyorrhexis.²⁰ No early developmental stage of the prehepatic generation of red cells is to be found in the fetal liver, fetal spleen or adult bone marrow.²² Thus it can be appreciated that embryonic blood during the prehepatic period furnishes a ready source of cells which are normally similar to the megaloblasts occurring in pernicious anemia. The importance of this is further emphasized by the fact that so far it has been either difficult²³ or impossible to produce by experimental methods²⁴ cells which are morphologically indistinguishable from the genuine megaloblasts occurring in pernicious anemia.¹⁶ Schwarz²⁵ expressed the opinion that the similarity of the embryonic cells to megaloblasts is due to the functionally undifferentiated liver present during the embryonic period; consequently the erythropoiesis is like that found in the marrow from patients with anemias due to liver principle deficiency. Because of these morphologic similarities the embryonic blood cells might react to various antianemic substances in a manner similar to that of the marrow cells in patients with pernicious anemia after specific antianemic therapy. Blood from 11 day rat embryos was considered appropriate for studies of this nature for several reasons.¹⁶ All of the hemoglobiniferous cells are nucleated. The chromatin is definitely stippled in a fairly coarse and irregular fashion, and the nucleoli are prominent. Marked nuclear condensation, pyknosis, karyorrhexis and karyolysis are either absent or extremely rare. Most of the cells have a highly basophilic cytoplasm. A fairly homogeneous population of cells like this should be suitable for determining the relative effects of erythrocyte-maturing factors on the nucleus, as well as on the cytoplasm. It might also serve to throw some light on such a controversial question as the fate of megaloblasts in cases of pernicious anemia after therapy. This has been supported, on the one hand, by Bock and Malamos,²⁶ Fieschi,²⁷ Jones,^{27a} Naegeli,²⁴ Rohr,²⁸ Segerdahl,²⁹ Storti³⁰

22. Bloom.¹⁹ Kirschbaum (footnotes 16 *f* and *g*).

23. Wills, L., and Stewart, A.: Experimental Anaemia in Monkeys with Special Reference to Macrocytic Nutritional Anaemia, *Brit. J. Exper. Path.* **16**: 444 (Oct.) 1935.

24. Naegeli, O.: Ueber die Entstehung und Behandlung der Anämien, *Wien. klin. Wchnschr.* **48**:225, 1935.

25. Schwarz, E.: Megaloblastische Blutbildung und Leber, *Wien. klin. Wchnschr.* **41**:192, 1928.

26. Bock, H. E., and Malamos, B.: Beiträge zur Megaloblastenfrage (Beobachtungen an Blut und Knochenmark im Verlaufe einer Ueberbehandelten Anaemia perniciosa), *Folia haemat.* **62**:408, 1939.

27. Fieschi, A.: Semeiologia del midollo osseo: Studio di morfologia clinica, in Ferrata, A.: Biblioteca "Haematologica," Pavia, Tipografia già Cooperativa, 1938, vol. 6.

27a. Jones (footnote 16 *a-d*).

and others, who have maintained that the megaloblasts occurring in patients with pernicious anemia complete their maturation as megalocytes and are not transformed into cells of the definitive, or normoblastic, series. On the other hand, Doan,³¹ Henning,³² Isaacs,³³ Lambin and de Weerd, ³⁴ Peabody,³⁵ Sabin and Miller,³⁶ Schulten ³⁷ and Schartum-Hansen ³⁸ have maintained that megaloblasts are transformed into cells of the normal, or definitive, series. Furthermore, Sabin ¹⁸ even expressed the belief that embryonic primitive erythroblasts (her original megaloblasts) serve as the precursors of normoblasts.

Undoubtedly, Wintrobe, Ivy and Higgins and their associates had in part somewhat similar aims as their ultimate goal when they undertook the studies of blood from the late fetus and newborn animal. However, these authors did not exercise the proper care in carrying over ideas obtained from studying anemias in the human being and applying them to the blood of the fetus and newborn of different animals. These difficulties have arisen primarily because quantitative studies of the blood picture have been emphasized to the almost complete exclusion of the qualitative studies. The macrocytic blood picture in the late stages of development of the pig and human fetuses studied by Wintrobe and Shumacker ³ is not produced by a megalocytosis similar to that seen in

28. Rohr, K.: Die diagnostische Bedeutung die Sternalpunktion, *Helvet. med. acta* **1**:713, 1935; *Knochenmarks-Morphologie des menschlichen Sternalpunktates*, Berlin, Urban & Schwarzenberg, 1937; *Das menschliche Knochenmark*, Leipzig, Georg Thieme, 1940.

29. Segerdahl, E.: *Ueber Sternalpunktionen*, Uppsala, Appelbergs Boktryckeri-aktiebolag, 1935.

30. Storti, E.: Studio in vivo del midollo osseo nell'anemia perniciosa, *Haematologica* **18**:1, 1937; La puntura sternale nella pratica clinica, *Gazz. d. osp.* **59**: 807, 1938.

31. Doan, C. A.: Bone Marrow: Normal and Pathologic Physiology with Special Reference to Diseases Involving the Cells of the Blood, in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 1839.

32. Henning, N.: Die Bedeutung der intravitalen Knochenmarksuntersuchung für die klinisch-hämatologische Diagnostik, *Deutsche med. Wchnschr.* **39**:1543, 1935; Ueber die bisherigen Ergebnisse der intravitalen Knochenmarksuntersuchung, *Med. Klin.* **16**:542, 1936.

33. Isaacs, R.: The Erythrocytes, in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 1, p. 1.

34. Lambin, P., and de Weerd, W.: Le problème des mégalo-blastes, *Rev. belge sc. med.* **10**:282 (April) 1938.

35. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, *Am. J. Path.* **2**:179 (May) 1927.

36. Sabin, F. R., and Miller, F. R.: Normal Bone Marrow, in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 1789.

37. Schulten, H.: Die Sternalpunktion als diagnostische Methode, Leipzig, Georg Thieme, 1937; Zum Megaloblastenproblem, *Folia haemat.* **57**:189, 1937.

38. Schartum-Hansen, H.: Zur Morphologie des Sternalpunktates bei perniziöser Anämie und makroblastischen Anämien, *Folia haemat.* **58**:145, 1937.

persons with pernicious anemia, for, contrary to Dameshek and Valentine³⁹ and others,⁴⁰ megaloblasts are not present in the fetal liver.¹⁰ The mere fact that normoblasts in the liver are larger than those in the adult bone marrow does not warrant the conclusion that they are megaloblasts. Cytologically the cells formed in the liver are quite different from megaloblasts and primitive erythroblasts.^{10f} On the other hand, if the macrocytic blood picture in the late stages of development of the pig and human fetus is likened to any anemia,⁴ it should be the macrocytic anemia seen in cases of atrophic hepatic cirrhosis in which there is a macronormoblastic marrow.⁴¹ Recently other authors,⁴² while emphasizing that liver principle-deficient anemias have a megaloblastic bone marrow, have pointed out that all megalocytic anemias are macrocytic but all macrocytic anemias are not necessarily megalocytic. Therefore, it would be unjustifiable to deduce the presence of megaloblasts in the hematopoietic organs or the qualitative identity of the blood pictures from the presence of a peripheral macrocytosis.⁴²

In the case of the blood from newborn rats, which Ivy and Higgins and their associates have used to study the effect of antianemic substances administered during gestation, there is a quantitative similarity to blood from patients with pernicious anemia, but qualitatively the two bloods are quite different. For example, in patients with pernicious anemia during relapse the percentage of reticulocytes is generally less than normal. These are almost exclusively products of the megaloblastic series and represent reticulated megalocytes. The macrocytosis in pernicious anemia is a megalocytosis which has resulted from the maturation of the pathologic megaloblastic series. On the other hand, in the blood of the newborn rat there are approximately 90 per cent or more reticulocytes.¹² When the sites of origin, conditions under which the cells are formed and the types of cellular precursors are considered, the macro-

39. Dameshek, W., and Valentine, E. H.: The Sternal Marrow in Pernicious Anemia: Correlation of the Observations at Biopsy with the Blood Picture and the Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, *Arch. Path.* **23**:159 (Feb.) 1937.

40. Aron, M.: L'origine du sang dans le foie embryonnaire chez les mammifères, *Arch. de morphol. gén. et expér.*, 1922, no. 10. Zanaty, A. F.: Erythrokon-ten und Erythropoese bei der Biermerschen Anämie und bei den Embryonen, *Virchows Arch. f. path. Anat.* **293**:794, 1934.

41. Benhamou, E.: Le traitement des anémies macrocytiques nou biermériennes, *Presse méd.* **47**:755 (May 17) 1939. Limarzi, L. R.: Diagnostic Value of Sternal Marrow Aspirations, *Illinois M. J.* **75**:38 (Jan.) 1939. Markoff, N.: Erythropoetische Knochenmarksfunction bei Lebercirrhose und Hämochromatose, *Deutsches Arch. f. klin. Med.* **183**:289 (Aug.) 1938. Revol, L.: L'exploration de la moelle osseuse par punction sternale, Paris, J. B. Bailliere et fils, 1938. Rohr.²⁸

42. (a) Davidson, L. S. P.: The Mechanism of Megaloblastic Blood Formation, *Edinburgh M. J.* **46**:474 (July) 1939. (b) Israels, M. C. G.: The Pathological Significance of the Megaloblast, *J. Path. & Bact.* **49**:231 (July) 1939.

cytosis in the blood of the newborn rat is qualitatively different from that in pernicious anemia. The newborn rat has some cells circulating in its blood which are the end products of those originally formed intravascularly in the yolk sac during the prehepatic period, large erythrocytes which are the products of large normoblasts formed extravascularly in the liver and erythrocytes formed from smaller normoblasts in the bone marrow, to say nothing of the spleen. Not only have all of these non-nucleated corpuscles been formed in different hematopoietic sites, but there is some evidence to indicate that their hemoglobins may differ.⁴³ If the antianemic principle which is effective in reducing the cell size in pernicious anemia does influence the blood picture of the newborn rat, it would be difficult to understand the actual mechanism involved in producing this reduction of cell size in the newborn rat. For example, the active agent might accelerate the erythropoiesis in the yolk sac; definitive, or normoblastic, cells might appear precociously; the size of cells formed in the liver might be decreased or erythropoiesis in the bone marrow and spleen might be stimulated.

MATERIAL AND METHODS

The pregnant rats, from which the 11 day embryos were obtained, originated from a strain of Wistar Norwegian white rats. The colony diet consisted of Purina dog chow (checkers)^{43a} supplemented by fresh green food biweekly. Females in the proper stage of estrus were each placed with a male shortly after midnight. The following morning at 9:30 a. m. vaginal smears were examined for the presence of sperm cells. If the latter were present, then this was taken as the starting point for timing the age of the embryos in days. Pregnant rats were placed in wire cages provided with feeding cups so constructed that the food could not be scratched out. Diets containing various percentages of desiccated stomach were made by using uniformly ground Purina dog chow (checkers) as a base to which 20 per cent by weight of ventriculin N. N. R. or ventriculin concentrate^{43b} was added. Other diets containing 10.0, 5.0, 2.5, 1.25 and 0.625 per cent, respectively, were made by attenuating the 20 per cent mixture.

All rats were killed by ether between 9:30 and 10:00 a. m. on the desired day of gestation. Since blood in the early stages of embryonic development does not lend itself readily to investigation by means of dry smears, the method of making dry smears of the yolk sac originally described by Kirschbaum⁴⁴ was utilized.

43. Brinkman, R., and Jonxis, J. H. P.: Occurrence of Several Kinds of Haemoglobin in Human Blood, *J. Physiol.* **85**:117 (Oct. 26) 1935.

43a. Purina dog chow (checkers) contains 21 per cent crude protein; 4 per cent crude fat; 6 per cent crude fiber and 46 per cent nitrogen-free extract. The ingredients are meat meal, dried skimmed milk, wheat germ, barley malt, dried beet pulp, corn grits, corn and wheat cereal feed, dried raisins, soy bean oil meal, molasses, riboflavin concentrate, carotene, dried brewers' yeast, cod liver oil, 1 per cent steamed bone meal and iodized salt.

43b. Ventriculin concentrate was obtained from Parke, Davis & Co.

44. Kirschbaum (footnotes 16f and g). Kirschbaum, A., and Downey, H.: A Comparison of Some of the Methods Used in Studies of Hemopoietic Tissues, *Anat. Rec.* **68**:227 (May) 1937.

The best preparations were obtained from the thinnest smears. Although it is desirable to make preparations with little or no maternal blood from the placenta, for practical purposes its presence is not a serious handicap, since embryonic cells cannot be confused with any of the cells in the maternal circulation. In a similar manner preparations with or without supravital and vital dyes were made for studying the living cells. Some embryonic vesicles were also fixed in Zenker's stock solution to which was added solution of formaldehyde U. S. P. (9:1), embedded in pyroxylin and stained with hematoxylin azure II and eosin.

Emphasis must be placed on the fact that the embryos implanted near the tubal extremity of the uterus are slightly more advanced in development than those near the cervix.⁴⁵ According to Mossman, this difference in development is roughly progressive from the one end of the uterine horn to the other. Hence, in sampling material for quantitative studies it is of the utmost importance that specimens are obtained from the tubal extremity of the uterus to the cervix and from each side. It should be pointed out at this time that the great variation in the physiologic macrocytosis within a given litter of newborn rats is due not to differences in the amount of antianemic principle available to each fetus from day to day, as suggested by Stasney, Higgins and Mann,⁴⁶ but to the difference in the length of time of implantation.^{45a}

In the present study, 100 cells and nuclei were measured from the yolk sac blood of at least 5 embryos. If more than one smear was made from a given yolk sac, then an equal number of cells and nuclei were measured from each. This was accomplished by using a slight modification of the Price-Jones method,⁴⁶ which consisted in outlining the cells and nuclei with a 6 H pencil by means of a camera lucida at a magnification of 1,000. Only cells from the thinnest portion of the smears were drawn. Care was exercised that well preserved, isolated, intact and properly flattened cells were drawn consecutively as they were encountered while the slide was being moved in an orderly fashion. The cell and nuclear outlines were measured with a glass millimeter scale graduated to 0.5 micron. The maximum and the minimum diameter through the center of the cell or nucleus were measured to 0.5 micron, and the mean of these two measurements was determined. The control series of mean cell and nuclear diameters was obtained by measuring 200 cells in the yolk sac blood from each of 28 embryos from 5 pregnant rats.⁴⁷ This series could not be used in the present quantitative study because there were differences in the time of mating the rats, their diets and the method of sampling blood from the embryos.

OBSERVATIONS

In the first series of experiments pregnant rats were fed diets containing 20 per cent by weight of desiccated stomach preparation because this diet was the one originally reported by Briese and Higgins.^{7a} Two

45. Mossman, H. W.: Comparative Morphogenesis of the Fetal Membranes and Accessory Uterine Structures, *Contrib. Embryol.* **26**:129 (Jan.) 1937.

45a. Jones, O. P.: The Degree of Macrocytosis in Blood from Newborn Rats as Related to the Time of Implantation, *Anat. Rec.* **79** (supp. 3):35 (March 25) 1941.

46. Price-Jones, C.: *Red Blood Cell Diameters*, London, Oxford University Press, 1933.

47. An additional control series of 5,000 cells from 14 embryos obtained from 9 pregnant rats (University of Minnesota stock) was used as a qualitative check.

rats (experiments 1 and 2) received ventriculin concentrate ^{47a} in their diets, and 6 rats (experiments 13 to 18) received regular ventriculin, or ventriculin N. N. R. When the mean cell and nuclear diameters had been calculated the results were found to be surprisingly unlike those

*Summary of Experimental Data**

Experiment No.	Rat No.	Body Weight, Kg.	Diet, Percentage of Ventriculin by Weight	Average Daily Dose Ventriculin, Gm.	Daily Dose Ventriculin, Gm. per Kg.	Mean Cell Diameter, Microns	Standard Deviation, Sigma (σ)	Critical Ratio	Mean Nuclear Diameter, Microns	Standard Deviation, Sigma (σ)	Critical Ratio
Control											
	14.44	1.42	9.29	1.01
Ventriculin Concentrate											
1	37B	0.302	20.0	3.43	11.4	14.42	1.39	0.4	9.14	0.96	3.3
2	41B	0.205	20.0	3.21	15.7	14.25	1.27	3.2	9.44	0.96	3.3
3	33B	0.219	10.0	1.62	7.4	13.72	1.36	11.4	8.79	0.94	11.2
4	70B	0.217	10.0	1.50	6.9	14.23	1.44	3.1	9.09	1.08	4.1
5	38B	0.219	5.0	0.78	3.6	14.35	1.40	1.6	9.25	0.98	0.8
6	44B	0.218	5.0	0.88	4.0	14.5	1.42	1.1	9.21	1.01	1.6
7	57B	0.263	2.5	0.45	1.7	13.75	1.30	11.4	8.88	0.91	9.6
8	54B	0.251	2.5	0.31	1.3	13.94	1.34	8.0	8.79	0.91	11.6
9	162	0.252	1.5	0.21	0.81	14.27	1.33	2.8	9.06	0.95	5.0
10	58B	0.200	1.25	0.18	0.89	13.69	1.35	11.9	8.72	0.99	12.2
11	69B	0.264	0.625	0.10	0.38	13.86	1.41	8.8	9.21	0.95	1.9
12	63B	0.253	0.625	0.10	0.39	14.55	1.43	1.5	9.61	1.01	6.6
Ventriculin N. N. R.											
13	34B	0.252	20.0	2.89	11.5	14.49	1.37	0.7	9.20	0.90	2.3
14	35B	0.277	20.0	3.66	13.2	14.43	1.54	0.3	9.73	1.12	8.5
15	39B	0.195	20.0	2.64	13.5	14.42	1.38	0.4	9.35	0.98	1.3
16	71B	0.222	20.0	3.29	14.8	14.84	1.67	5.3	9.55	1.14	5.0
17	73B	0.231	20.0	2.67	11.6	14.72	1.65	3.7	9.61	1.11	6.3
18	91B	0.247	20.0	3.30	13.3	14.87	1.65	5.6	9.36	0.98	1.5
19	69B	0.217	10.0	1.49	6.9	14.05	1.31	6.3	9.08	0.85	4.9
20	94B	0.179	5.0	0.87	4.9	14.34	1.39	1.5	9.05	0.99	5.2
21	95B	0.211	5.0	0.90	4.3	14.36	1.45	1.2	9.31	1.00	0.4
22	160	0.261	5.0	0.75	2.8	14.48	1.44	0.6	9.07	0.96	4.9
23	153	0.236	2.5	0.44	1.8	14.12	1.38	5.0	9.07	0.89	5.3
24	59B	0.291	2.5	0.52	1.8	13.42	1.22	17.6	8.81	1.00	10.2
25	75B	0.279	1.25	0.25	0.89	14.19	1.32	4.0	8.88	0.86	10.3
26	72B	0.202	1.25	0.19	0.96	13.95	1.37	7.9	9.16	0.99	2.9
27	49B	0.290	0.625	0.11	0.37	14.31	1.43	2.4	9.01	1.03	5.8
28	66B	0.192	0.625	0.10	0.50	14.13	1.46	4.6	9.16	1.11	2.5
Ventriculin and Liver Extract											
29	68B	0.190	20.0	2.18	11.5	14.41	1.43	0.6	9.19	0.96	2.2
30	74B	0.197	20.0	2.40	12.2	14.25	1.37	3.0	8.97	1.02	6.6

* The figures set in bold-faced type indicate the mean diameters which were significantly decreased from the normal mean and their critical ratios.

anticipated from the work of Briese and Higgins.^{7a} Data in the table show that neither the cell nor the nuclear diameters of the embryonic blood cells were significantly decreased by the diets containing regular

47a. The ventriculin concentrate was obtained in the form of R 924959, from Parke, Davis & Co. This preparation is three to four times more effective than ventriculin N. N. R. as measured by the daily dose required for induction of remission in a case of severe relapse of pernicious anemia.

ventriculin. There was, however, a slight but significant change in these diameters when the diets contained 20 per cent ventriculin concentrate.

In order to compare the daily dosage of stomach preparation fed to the pregnant rats with that administered during relapse to patients with pernicious anemia, it was considered more accurate to use the mean body weight of the latter group than a mean of the body weight of normal adult human beings. Dr. Raphael Isaacs furnished this information from the records of the Simpson Memorial Institute, Ann Arbor, Mich. The arithmetic mean of the body weight of 500 patients was 133.58 pounds, or 63 Kg. Since regular ventriculin is standardized so that the daily oral administration of 30 Gm. will induce a remission, this value was selected as the maximum human dose. In this case the average human dose is 0.48 Gm. per kilogram of body weight. It is obvious from data in the table that pregnant rats which were fed diets containing 20 per cent ventriculin, as reported by Briesse and Higgins,^{7a} were receiving twenty-three to thirty times the maximal human per kilogram daily dose. Although it was known that such a nonphysiologic diet might be causing the loose stools and diarrhea present in most of these rats, the exact relation of these two factors with the lack of a decrease in the diameters of embryonic blood cells was not recognized at this time. Data in the table show that there was a significant decrease in both the cell and the nuclear diameters of blood cells from embryos from pregnant rats (experiments 3, 4 and 19) fed diets containing 10 per cent ventriculin or ventriculin concentrate. These changes with the 10 per cent mixtures were so constant and significant that diets containing smaller quantities of desiccated stomach were tried. The table shows that a significant change in either the cell and/or the nuclear diameters was obtained when the diets contained 5.0, 2.5, 1.5, 1.25 and 0.625 per cent desiccated stomach. Lesser concentrations were not tried because the last-named amount appeared to be a suboptimal quantity. It will be noted that embryos from rats in experiments 5 and 6, which were fed a diet with 5 per cent ventriculin concentrate, did not have a significant change in the size of blood cells. This may be partly accounted for on the basis of inadequate and faulty sampling, which was due to the accidental bursting of embryonic vesicles from the tubal extremity of the uterus, thereby making it impossible to get a good series of representative preparations.

Data in the table and figure 1 show that as a rule diets containing the lesser quantities of gastric preparation influenced embryonic erythropoiesis more efficaciously than those containing higher concentrations. This is further emphasized in the following experiments, the results of which are shown in figure 2. Litter mate rats (experiments 16 and 26) were successfully bred on the same night. The following

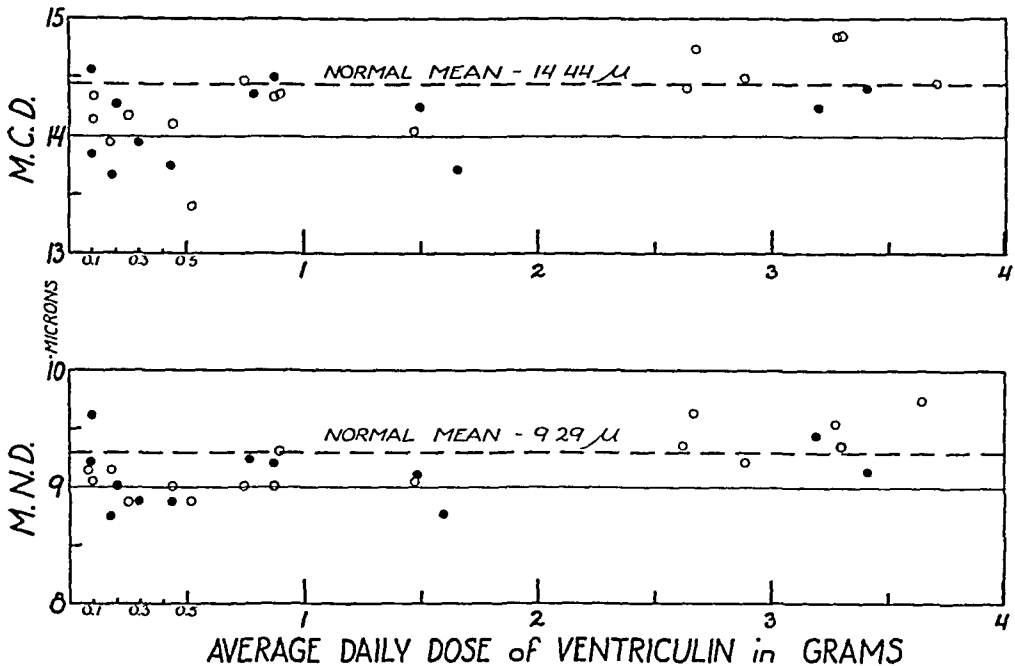


Fig. 1.—The circles represent the mean diameter of cells (M.C.D.) and nuclei (M.N.D.) of blood obtained from embryos from pregnant rats fed diets containing ventriculin. The dots represent the mean diameters of blood cells from embryos from pregnant rats receiving ventriculin concentrate.

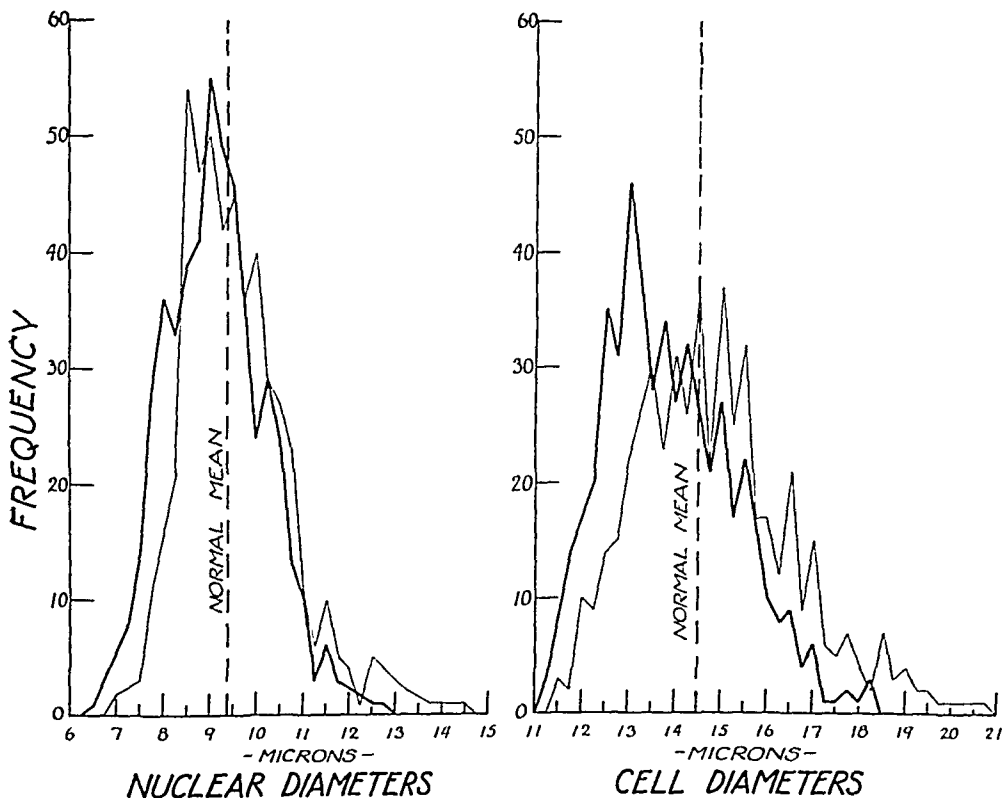


Fig. 2.—The heavy line represents the diameter of blood cells from embryos from a pregnant rat (72 B) fed a 1.25 per cent ventriculin diet. The thin line shows the diameters of cells obtained from blood of embryos from a pregnant rat (71 B) fed a 20 per cent ventriculin diet.

morning one rat was started on a diet containing 20 per cent ventriculin and the other on a diet containing 1.25 per cent ventriculin. The data in the table and the frequency distribution curves of figure 2 show that blood cells from embryos from a pregnant rat fed the latter diet had a significant decrease in the mean cell and nuclear diameters. Similar values for blood cells from embryos from the pregnant rat fed a 20 per cent ventriculin diet were not decreased, but were greater than normal. The same type of reaction was obtained in experiments 18 and 25, which also ran concurrently. These differences might have been attributed to the injurious effects of an excessive amount of antianemic substance⁴⁸ on embryonic erythropoiesis if it were not for the fact that rats fed a 20 per cent ventriculin diet had some gastrointestinal disturbance which manifested itself as loose stools or diarrhea. Castle and others have presented evidence indicating that in cases of macrocytic anemia the absorptive capacity of the intestine for antianemic substances may gradually fail⁴⁹ even until there is complete resistance to the oral administration of liver extract⁵⁰; it may be diminished by obstruction, intestinal anastomoses⁵¹ and acid mixtures of intrinsic and extrinsic

48. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies, *Ann. Int. Med.* **3**:216 (Sept.) 1929.

49. (a) Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or With Hypochromic Anemia Having No Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, *Am. J. M. Sc.* **182**:741 (Dec.) 1931. (b) Castle, W. B.; Rhoads, C. P.; Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue: Observations on Patients in Puerto Rico and Subsequent Experiments on Animals, *Arch. Int. Med.* **56**:627 (Oct.) 1935. (c) Castle, W. B.; Townsend, W. C., and Heath, C. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *Am. J. M. Sc.* **180**:305 (Sept.) 1930. (d) Isaacs, R.; Sturgis, C. C.; Goldhamer, S. M., and Bethell, F. H.: The Use of Liver Extract Intravenously in the Treatment of Pernicious Anemia, *J. A. M. A.* **100**:629 (March 4) 1933.

50. Minot, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions: Their Value in Determining the Potency of Therapeutic Materials, Especially in Pernicious Anemia, *Lancet* **2**:319 (Aug. 10) 1935.

51. (a) Barker, W. H., and Hummel, L. E.: Macrocytic Anemia in Association with Intestinal Strictures and Anastomoses: Review of the Literature and Report of Two New Cases, *Bull. Johns Hopkins Hosp.* **64**:215 (April) 1939. (b) Castle, Heath and Strauss.^{49a} (c) Little, W. D.; Zerfas, L. D., and Trusler, H. M.: Chronic Obstruction of the Small Bowel the Result of Two Enterenterostomies and Apparently the Cause of Pernicious Anemia, *J. A. M. A.* **93**:1290 (Oct. 26) 1929.

factors,⁵² and, finally it may be altered by diarrhea⁵³ or changes in the intestinal wall itself.^{49b} However, Barker and Rhoads⁵⁴ expressed the belief that malabsorption in patients with sprue results in diarrhea, and is not produced by it. In addition to malabsorption of antianemic substance, that of the carbohydrates⁵⁵ and fats⁵⁴ has also been reported.

The fact that a 20 per cent ventriculin diet was ineffective whereas a 1.25 per cent ventriculin diet stimulated embryonic erythropoiesis, has a counterpart in the case report by Isaacs and associates.^{49d} The essence of the report is that a man aged 22 with a history of pernicious anemia beginning four years previously did not respond to administration of desiccated hog stomach in doses up to 150 Gm. daily. During a subsequent relapse he was given 40 to 50 Gm. of desiccated hog stomach, which produced a markedly submaximal response. Since this patient responded early in the course of his disease to the juice from 1 to 3 pounds (453 to 1,306 Gm.) of liver a day and later gave only a submaximal response to 40 to 50 Gm. of stomach preparation, it might be assumed that this was caused by a progressive development of defective absorption of hematopoietic substances.⁴⁹ In view of the negative results obtained when pregnant rats were fed diets rich in ventriculin, it might also be that the patient of Isaacs and associates^{49d} did not respond to the dose of 150 Gm. of stomach preparation daily because of the changes produced in the intestinal wall due to the massive doses of the preparation.

In the rat these changes consisted of a decreased number of goblet cells and an increase of lymphoid cells in the lamina propria of the cores of villi. These cells were chiefly small and medium-sized lymphocytes and polyblasts. In some sections the number of globular leukocytes was striking. Because the material was stained only with hematoxylin-triosin after fixation in Bouin's fluid, it was impossible to determine whether the high ventriculin diet caused the transformation of polyblasts into basophil myelocytes, which has been reported in guinea pigs after subcutaneous injection of autoclaved ventriculin (a 5 per cent suspension in Tyrode solution without sodium bicarbonate).⁵⁶ Furthermore, it was

52. Castle, W. B.; Heath, C. W.; Strauss, M. B., and Heinle, R. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: VI. The Site of the Interaction of Food (Extrinsic) and Gastric (Intrinsic) Factors; Failure of in Vitro Incubation to Produce a Thermostable Hematopoietic Principle, *Am. J. M. Sc.* **194**:618 (Nov.) 1937.

53. Castle, Heath and Strauss.^{49a} Castle, Rhoads, Lawson and Payne.^{49b}

54. Barker, W. H., and Rhoads, C. P.: The Effect of Liver Extract on the Absorption of Fat in Sprue, *Am. J. M. Sc.* **194**:804 (Dec.) 1937.

55. Hanes, F. M., and McBryde, A.: Identity of Sprue, Nontropical Sprue and Celiac Disease, *Arch. Int. Med.* **58**:1 (July) 1936.

56. Plimpton, N. C.: Basophil Leucocytes and Myelocytes After Local Injection of Ventriculin, *Anat. Rec.* **76**:475 (April) 1940.

also impossible to determine whether this type of diet would cause the argentaffine cells to increase, as implied in the recent work by Jacobson.⁵⁷

Castle and Ham⁵⁸ have schematically represented the factors which are concerned with the production of the antianemic principle: $\frac{F \times G}{I} = \text{L.E.}$ In this formula, F stands for food (extrinsic) factor, G for gastric (intrinsic) factor, I for intestinal impermeability and L.E. for liver extract. A similar scheme can be used to represent the relation of the several factors concerned with the absorption of some antianemic substance from the maternal gastrointestinal tract and its subsequent influence on embryonic erythropoiesis. Instead of expressing intestinal absorption in terms of impermeability (I), for the sake of clarity I find it is more appropriate to let I equal $\frac{1}{P}$, P standing for intestinal permeability. In this case Castle and Ham's equation can be expressed as L.E. equals $F \times G \times P$. Furthermore, if a reduction in the mean cell and nuclear diameters of the primitive erythroblasts of embryonic blood is used to indicate the effectiveness of some antianemic substance absorbed from the maternal gastrointestinal tract and transmitted across the placenta, then it should follow that L.E. equals $\frac{1}{\text{M.D.}}$, M.D. being mean diameter. It is, of course, understood that the L.E. of Castle and Ham's equation is not necessarily identical with the antianemic substance acting on the embryonic blood cells, but both substances do have the property of reducing cell size. Substituting these values in the original equation, then $\text{M.D.} = \frac{1}{F \times G \times P}$. When normal pregnant rats are fed diets containing ventriculin, the factor ($F \times G$) is constant for any one animal during the experiment, since the antianemic activity of ventriculin depends on both the thermostable (extrinsic) and the thermolabile (intrinsic) factor.⁵⁸ If the factor ($F \times G$) is increased, by feeding larger amounts of ventriculin, while M.D. remains the same or even increases, then the factor P must necessarily have decreased. Data in the table and in figures 1 and 2 indicate that some factor of intestinal permeability decreased with the higher concentrations of ventriculin after the maximum cell-reducing and nucleus-reducing effects have been obtained. In other words, ($F \times G$) can be increased up to a certain point, with a resultant decrease in M.D., but beyond the maximum effective dose higher concentrations of ventriculin have little or no effect on the blood cells of the embryo because of the decreased permeability

57. Jacobson, W.: The Argentaffine Cells and Pernicious Anaemia, *J. Path. & Bact.* **49**:1 (July) 1939.

58. Castle, W. B., and Ham, T. H.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: V. Further Evidence for the Essential Participation of Extrinsic Factor in Hematopoietic Responses to Mixtures of Beef Muscle and Gastric Juice and to Hog Stomach Mucosa, *J. A. M. A.* **107**:1456 (Oct. 31) 1936.

produced by such a diet. Data in the table also indicate that the mean diameters of embryonic blood from rats in experiments 16 to 18 were significantly increased from the normal mean. This might be interpreted to indicate that factor P was decreased to such an extent that the mother was not even absorbing amounts of food and antianemic substance necessary for normal embryonic erythropoiesis in spite of a superabundance of ventriculin in the diet.

It is known that intestinal permeability may be markedly influenced by increased peristalsis and diarrhea, with a resultant malabsorption of substances from the intestine.⁵⁹ It should, therefore, be possible to predict a priori (according to the aforementioned equations) whether maximal or minimal changes are to be expected in a given experiment by observing the consistency of the stools. Experiments 20 and 21 ran concurrently, and it was noted that the rat in the latter experiment had stools which were loose as compared with those of the rat in the former experiment, which were quite normal. Before the termination of these experiments it was anticipated that the blood cells from the embryos from the rat with the loose stools would not be decreased to the same extent as those in the other experiment. Data in the table show that the nuclear diameters were significantly decreased in experiment 20, whereas the cell and nuclear diameters remained unaltered in experiment 21. In experiments 22 and 23, which also ran concurrently, it was anticipated that the changes in the former would not be maximal, since the rat had soft stools. Data in the table support this supposition. In experiment 9 the changes in the mean diameters were not as great as those in experiments 8 and 10, and the rat in this experiment also had slightly loose stools. It will be noted that the gastrointestinal tract of rats fed identical diets reacted differently. In the case of rats which were fed 20 per cent regular ventriculin (experiments 13 to 18) it is significant that the trend of the mean diameters was constantly normal or greater than normal and that in most of these animals the diarrhea was pronounced.

It might be argued that a diet containing 20 per cent ventriculin fed to pregnant rats has no influence on erythropoiesis in the 11 day rat embryo because of its deleterious effect on the placenta rather than its malabsorption from the intestine (fig. 3). On the other hand, if a barrier has been created in the maternal intestinal wall by a diet containing 20 to 30 times the maximal human per kilogram daily dose of desiccated stomach, then the placenta should be unaffected and transmit antianemic substances administered through another route—the intramuscular. The

59. Castle, Heath and Strauss.^{49a} Castle, Rhoads, Lawson and Payne.^{49b} Davidson.^{42a}

following experiments were devised to test these two points. Pregnant rats (experiments 17, 29 and 30) were fed a 20 per cent ventriculin diet, which previous experiments have demonstrated to be ineffective in influencing embryonic erythropoiesis in spite of the superabundance of antianemic substance in the maternal gastrointestinal tract. This diet was continued throughout the first eleven days of pregnancy. On the seventh, eighth, ninth and tenth days of pregnancy the rat in experiment 29 was given an intramuscular injection of 1 cc. of concentrated liver extract.^{59a} The reasons for administering liver extract intramuscularly on these particular days were twofold. First, it was thought that after the rat had consumed the 20 per cent ventriculin diet for a week intestinal malabsorption should be well established. Second, the seventh to tenth days of pregnancy are before and during the first period of embryonic erythropoiesis.^{16d} At the same time another pregnant rat (experiment 17) was fed the 20 per cent ventriculin diet, but it did not receive liver extract intramuscularly. Data in the table show that although the mean cell and nuclear diameters of blood cells from embryos out of the rat



Fig. 3.—A schematic representation of the barriers antianemic substance must cross in a pregnant animal before it can influence embryonic erythropoiesis.

in experiment 29 which received ventriculin and liver extract were much less than those in the embryos from the rat in experiment 17, they were not significantly shifted from the normal mean. However, the nuclear size did show a trend in the direction of reduction. These negative results were not interpreted to indicate a faulty placental barrier, since the liver extract was not a regular clinically tested and approved product and the animal did not tolerate well such a massive dose. These massive, nonphysiologic doses of liver extract were used because the amount metabolized and excreted by the mother is unknown, the degree of placental permeability to antianemic substances is unknown and, if the placenta is permeable, at least a dozen embryos have to have an amount sufficient to be effective. Finally, large doses of antianemic substances might cause the precocious appearance of normoblasts. Rat 74 B was treated in the same manner, except that it received intra-

59a. The concentrated liver extract was obtained from Parke, Davis & Co. for investigational purposes only.

muscularly 2 cc. of regular liver extract ^{59b} on the seventh and ninth days of gestation. Data in the table show that both the mean cell and the nuclear diameter of the embryonic blood cells were significantly decreased from the normal mean. When these values are plotted against a frequency distribution curve of the cell and nuclear diameters of blood from all embryos from rats fed a diet of 20 per cent ventriculin (fig. 4), it is evident that some antianemic substance from the liver extract given intramuscularly must have been transmitted across the placenta, which was still permeable. The latter fact agrees with the results obtained in previous experiments.^{16d} It has been pointed out by Barker and asso-

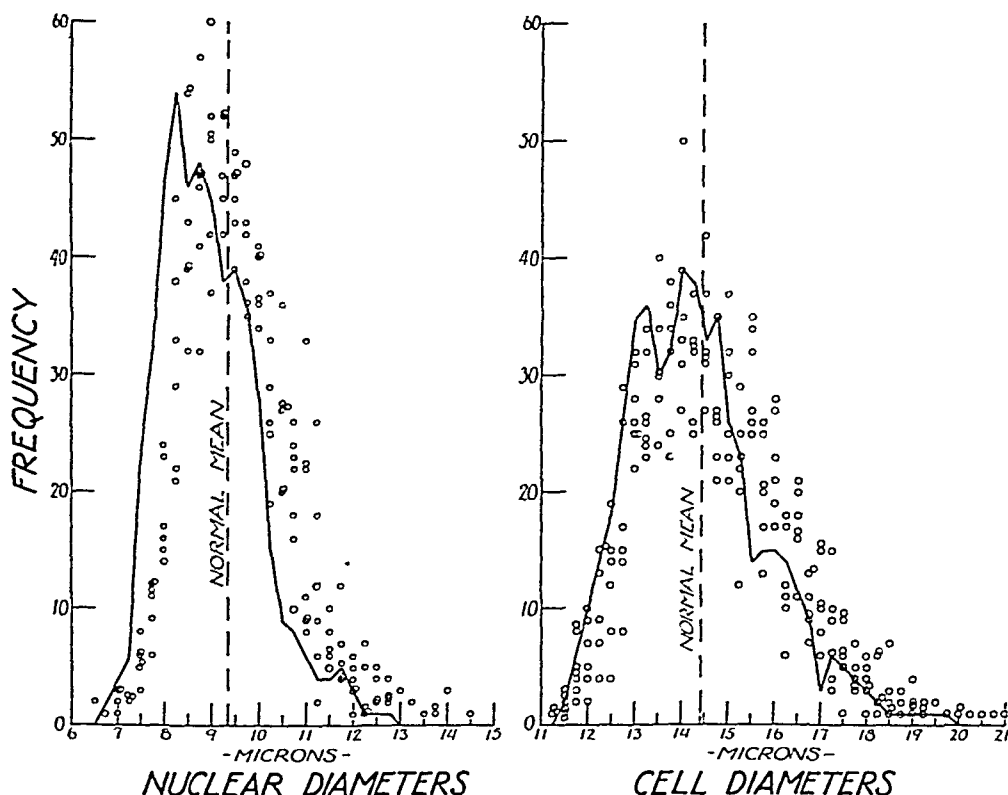


Fig. 4.—The circles represent the diameters of blood cells from all embryos from pregnant rats (experiments 13 to 18) fed a 20 per cent ventriculin diet. The solid line indicates the diameters of blood cells from embryos from a pregnant rat (experiment 30) receiving a 20 per cent ventriculin diet and parenteral injections of liver extract on the seventh and ninth days of gestation.

ciates ⁶⁰ that injections of liver extract may increase the permeability of the intestine for certain food substances in some macrocytic anemias. If this condition obtains for the normal pregnant rat in experiment 30 fed a diet of 20 per cent ventriculin and given injections of liver extract,

59b. The regular liver extract was obtained in the form of liver extract (intramuscular)—Parke, Davis & Co.

60. Barker and Hummel.^{51a} Barker and Rhoads.⁵⁴

then it would be difficult to ascertain how much of the cell-reducing effect was produced by the liver extract given intramuscularly and how much by the antianemic substance absorbed from the gastrointestinal tract after the permeability had been increased. In view of the relatively short time elapsing between the injections of liver extract and the termination of the experiment, and of the fact that intramuscular injections of liver extract alone will produce similar changes,^{16d} the effect on embryonic erythropoiesis is perhaps for the most part due to something in this substance. These experiments indicate that high concentrations of ventriculin are ineffective because of a barrier which has been created in the intestinal wall and that the placenta will transmit antianemic substance providing it is made available through the maternal blood stream (fig. 3). Even if loose stools, diarrhea and mild enteritis were not present in the rats fed high concentrations of ventriculin, one would arrive at the conclusion that there is a physiologic barrier created in the intestinal wall and that the placenta is unaffected.

COMMENT

The present studies are not the first to demonstrate that some anti-anemic principle can accelerate the development of primitive erythroblasts in the embryo. Cohn and associates⁶¹ furnished Sabin with fraction R of liver extract, which she added to living chick blastoderms mounted in Locke's solution. In these preparations mitoses were accelerated in the endothelium and in the cells which Sabin¹⁸ originally interpreted as megaloblasts. Reimer,⁶² who injected various liver preparations diluted with physiologic solution of sodium chloride into chicken eggs incubated for three to seventeen days, was unable to find any qualitative or quantitative changes in the blood. He did observe nonspecific degenerative changes in the liver, which indicated that at least the material had been absorbed by the embryo. However, the present studies are the first to demonstrate that primitive erythroblasts of mammalian embryos can be influenced by some antianemic substance transmitted across the placenta.⁶³ The observations by Sabin,⁶¹ cited by Cohn and associates, and the results of the present study support the concept that some antianemic substance acts directly on the primitive red cells, perhaps by supplying a building stone for their proper maturation. In contrast to this, Barker and Hummel^{51a} have made some interesting tentative assumptions regarding the possible

61. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia: II., *J. Biol. Chem.* **77**: 325 (May) 1928.

62. Reimer, L.: Versuche zur Beeinflussung der Blutbildung beim Hühner-embryo durch Antiperniciosastoff, *Arch. f. exper. Path. u. Pharmakol.* **189**:656, 1938.

63. Jones (footnotes 16d and e).

action of liver principle in treatment of macrocytic anemia. For example, they claimed that the active principle might act on a normally functioning liver and promote the detoxification of injurious substances which had prevented normal erythropoiesis. The studies of both Sabin, cited by Cohn and associates,⁶¹ and Jones⁶³ on the influence of antianemic substances before and during the prehepatic period of embryonic development certainly would indicate that this principle can exert its influence in the absence of a functioning liver. If the assumption made by Barker and Hummel^{51a} is correct, then prehepatic embryonic erythropoiesis, which stimulates, but is not identical with, that in pernicious anemia, is due to the absence of detoxifying powers normally possessed by the liver.

Although the results in the present study seem to contradict those reported by Briese and Higgins,^{7a} it must be borne in mind that the two experiments are quite different with respect to the duration of the experiment and nature of the blood cells measured. It is not unlikely that the intestinal impermeability created by diets of 20 per cent ventriculin during the first eleven days of pregnancy might break down when the rats are fed this diet throughout the entire period of gestation. And, then, other sites of erythropoiesis, such as the liver, the spleen and the bone marrow, may be more labile in their response than the yolk sac. In the present report the decrease in cell and nuclear diameters is due to an acceleration of cytoplasmic differentiation and nuclear maturation of the primitive erythroblasts. It has been mentioned in the first part of this paper that the decrease in the size of blood corpuscles from newborn rats reported by Briese and Higgins^{7a} is difficult to analyze, since the yolk sac, liver, spleen and bone marrow may not respond alike and to the same degree. The results obtained by Briese and Higgins^{7a} may be due to stimulation of erythropoietic foci of normoblasts (definitive erythroblasts).

Also, it should be strongly emphasized that so far it has been impossible to cause a transformation of primitive erythroblasts (Sabin's megaloblasts)¹⁸ into normoblasts or cells of the definitive series.⁶³ This is based on a consideration of cell size, nucleocytoplasmic ratio and nuclear structure. This lends some support to the view held by those who have maintained that the megaloblasts occurring in pernicious anemia complete their maturation as megalocytes and are not transformed into cells of the normoblastic series after antianemic therapy.⁶⁴

If a decrease in the mean diameters of embryonic blood cells is used to indicate the effectiveness of antianemic substance absorbed from the maternal gastrointestinal tract, then, according to data in the table, impermeability of the intestinal tract to antianemic substance did not commence to increase appreciably until the rats were fed a daily dose of

64. Bock and Malamos.²⁶ Fieschi.²⁷ Jones.^{27a} Naegeli.²⁴ Rohr.²⁸ Segerdahl.²⁹ Storti.³⁰

ventriculin equivalent to 6 Gm. per kilogram of body weight. This is roughly twelve times the human dose per kilogram of body weight. In the case reported by Isaacs and associates,^{40d} the patient did not respond even after receiving a daily dose five times the usual maximum human dose. This increased malabsorption in the human subject may be due to the gradual failure of the absorptive capacity of the intestine for anti-anemic substances in macrocytic anemias.⁶⁵ Or it may be due to changes produced in the intestinal wall by the drug itself. In the rat the intestinal impermeability does not make its appearance until at least three times the maximal effective dose of ventriculin has been administered. Unfortunately, there are no data in the literature at present concerning how large a dose of desiccated hog stomach can be administered to a patient with pernicious anemia before malabsorption of this antianemic substance is set up by the mild enteritis.⁶⁶ It is also possible that the latter is produced in the pregnant rat and not in the human subject.

In view of the fact that slight excesses of antianemic substance in the diets of pregnant rats will accelerate embryonic erythropoiesis, it is of interest to note that Ritter and Crocker⁶⁷ reported a macrocytic anemia of pregnancy and an anemia of the newborn which were possibly due to the same dietary deficiency in the mother.

CONCLUSIONS

1. When normal pregnant rats are fed diets containing desiccated hog stomach, some antianemic substance absorbed from the gastrointestinal tract is transmitted across the placenta and influences prehepatic embryonic erythropoiesis.

2. Diets containing high concentrations of desiccated hog stomach are not as effective as those containing amounts nearer physiologic limits because of the increased intestinal malabsorption produced by the diet itself.

3. The effectiveness of antianemic substance after it has crossed the placenta is indicated by a reduction in the mean cell and nuclear diameters of the primitive erythroblasts of embryonic blood. In general, ventriculin concentrate is more effective than regular ventriculin.

4. On the basis of their nuclear pattern, cell size and nucleocytoplasmic ratio, cells of the first, or primitive, generation have not been trans-

65. Castle and others.⁴⁹ Minot and Castle.⁵⁰

66. In a recent article Morrison has stated that intestinal permeability is an important and uncertain factor in determining the potency of oral preparations (Studies in Pernicious Anemia: An Inquiry into the Rôle of Pepsin, *Ann. Int. Med.* **14**:242 [Aug.] 1940).

67. Ritter, J. A., and Crocker, W. J.: Macrocytic Anemia of the Newborn, *Am. J. Obst. & Gynec.* **38**:239 (Aug.) 1939.

formed into cells of the second, or definitive, generation; however, their maturation has been accelerated.

NOTE.—After this manuscript was submitted for publication, two articles were published which seemed to nullify the interpretation of the foregoing results. This would be of great import if it were not for the fact that these two pieces of research are based on unsound premises. Last and Hays have reported that potent liver extract administered to pregnant rats did not increase the percentage of non-nucleated corpuscles in the blood of the 15 day rat fetus (*Effect on Blood Picture of 15-Day Embryo of Liver Extract Injected into Pregnant Rats*, *Proc. Soc. Exper. Biol. & Med.* 46: 194 [Jan.] 1941). It does not necessarily follow that accelerated erythropoiesis in the 11 day embryo should be reflected in the blood on the fifteenth day by an increment of the non-nucleated corpuscles. Cytoplasmic differentiation and nuclear maturation do not proceed at the same rate. It is unfortunate that Last and Hays studied blood from 15 day fetuses, since slight, or even significant, changes in cells of the prehepatic generation are apt to be attenuated or completely masked by the rapidly growing normoblastic generation. This is the very thing which was specifically avoided in my studies of yolk sac blood from the 11 day embryo. Last and Hays have also reported that potent liver extract and ventriculin administered to pregnant rats “cannot” influence the maturation of primitive erythropoiesis of the 11 day rat embryo as determined by measuring the nuclear diameters (*The Effect on the Blood Picture of the 11 Day Embryo of Liver Extract Injected into the Pregnant Rat*, *J. Pharmacol. & Exper. Therap.* 72: 25 [May] 1941). Here, again, it is unfortunate that these authors did not know that nuclear diameters are not decreased to the same degree as cell diameters after the administration of antianemic substances to the pregnant rat. Since the changes in cell diameters are more pronounced and since there is a greater percentage of error in measuring the smaller nuclear diameters, the latter have been completely discarded in my more recent studies. Although the quantitative changes seem small, there are certain qualitative changes which support my contention that there is a placental transfer of some antianemic principle. These will be reported on separately in the future.

Material was furnished by Dr. E. A. Sharp, of Parke, Davis & Co.; A. B. Constantine helped with the statistical analyses, and valuable personal communications were furnished by Dr. George M. Higgins, of the Mayo Clinic. The technical assistance furnished by R. Ament, A. B. Constantine and A. Seeger was made possible through the National Youth Administration.

STATE OF MOTOR CENTERS IN CIRCULATORY INSUFFICIENCY

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AND

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In a previous communication by an associate and us¹ the fusion frequency of flicker was reported as decreased in circulatory insufficiency (hypertension or heart disease). This decrease is probably due to a reduced oxygen supply to the central nervous system. Fatigue develops first in the sensory centers, and it spreads from there to involve other parts of the central nervous system. Visual centers are especially sensitive to the lack of oxygen. Hence the use of the fusion frequency of flicker might be expected to uncover changes not detectable by other methods. (For a review of pertinent literature, see the previous communication.¹)

The effect of fatigue on the motor centers has much practical significance, and its measurement is important, since, after all, "performance" is the objective clinical evidence of fatigue. Therefore, a combined investigation of a sensory and a motor function should enable us to come to some conclusions about the extent of the pathologic alterations in the central nervous system.

In order to obtain data directly comparable to those from investigations on the fusion frequency of flicker, we studied the maximum frequency of motor impulses.

As possibly the simplest method for determining the maximum frequency of motor impulses, we chose the measurement of the maximum frequency of finger movements. The findings of different authors²

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1. Simonson, E.; Blankstein, S., and Enzer, N.: The Fusion Frequency of Flicker in Circulatory Insufficiency, *Ann. Int. Med.*, to be published.

2. Bruecke, F.: Die Nerven-Chronaxie als Funktion der Reizfrequenz, *Arch. f. d. ges. Physiol.* **233**:777, 1934. Raevsky, V. S., and Babdyanyane, M.: Influence du rythme du travail sur les changements de la chronaxie musculaire, *Bull. biol. et méd. expér. URSS* **5**:482, 1938. Lapique, L.: Rapport de la chronaxie à la vitesse du mouvement dans divers tissus excitables, *Compt. rend. Soc. de biol.* **128**:688, 1938. Freeman, R. G., Jr., and Wechsler, D.: Note on the Correlation Between Chronaxie and Reaction Time, *Proc. Soc. Exper. Biol. & Med.* **29**:957, 1932. Latmanizova, L. F.: Chronaxie of Neuromuscular Apparatus in Conditions of Rhythmic and Non-Rhythmic Stimulation, *Bull. biol. et méd. expér. URSS* **6**:540, 1938. Hayasi, K., and Bruecke, E. T.: Ueber die Abhängigkeit der Nerven-Chronaxie von der Reizfrequenz, *Arch. f. d. ges. Physiol.* **235**:31, 1934.

indicate a close relation between chronaxia, the maximum frequency of discharge of the motor centers, and the speed or frequency of movements. As the weight of the fingers, and consequently the inertia in finger movements, is small, the relation between the maximum frequency of finger movements and the maximum frequency of the actual number of motor impulses is close. Lehmann³ has shown that the number of motor impulses is directly proportional to the speed of finger movements. The actual frequency of motor impulses in voluntary movements is higher than this method would reveal—according to the latest data of Bouman and van Rijnberk⁴ about four to six times and according to the data of Simpson and Derbyshire⁵ about one and a half times.

The performance of this test does not depend on any peripheral function; the increase of metabolic processes is slight; there is no demand for any considerable blood supply, and there are no such disagreeable sensations as characterize static work. The test measures function of the motor centers. The purpose of this study was to investigate the fundamental processes of fatigue and of adaptation of motor centers in circulatory insufficiency.

METHOD

The subject stood in front of a table on which an impulse counter was placed. He touched the button of the counter with his middle finger "as fast as possible." Before the recorded test the subject was given several trial tests in order to familiarize him with the technic. After that, he was asked to begin and to continue "until the stop signal," which was given after one minute. The number of contacts was registered each ten seconds by means of a stopwatch; thus, the values are expressed as the number of motor impulses per ten seconds.

The following values seem to be especially important: the maximum frequency, normally obtained in the beginning; the minimum frequency, to which the number of impulses drops during the test, and the difference between the maximum and the minimum frequency.

The test was repeated after a pause of one minute, in order to investigate the possible influence of adaptation. Comparison of the values of the first and the second performance could show a prevailing fatigue or a prevailing adaptation; in the first case the values of the second performance must be lower, and in the latter case higher, than those of the first performance. The test was performed first with the right hand and then with the left.

3. Lehmann, G.: Ueber den Mechanismus bei Willkürbewegung, *Arbeitsphysiol.* **1**:1, 1928.

4. Bouman, H. D., and van Rijnberk, G.: On Muscle Sound Produced During Voluntary Contraction in Man, *Arch. néerl. de physiol.* **23**:34, 1938.

5. Simpson, H. N., and Derbyshire, A. J.: Electrical Activity of the Motor Cortex During Cerebral Anemia, *Am. J. Physiol.* **109**:99, 1934.

Values were obtained for 42 normal subjects from 20 to 64 years of age. Twenty-three patients with hypertension or heart disease were studied. In 19 of the patients the fusion frequency of flicker was measured.¹

Patient	Age	Sex	Comment
1	28	F	Fully compensated mitral stenosis
2	17	F	Compensated mitral stenosis complicated by pregnancy
3	54	F	Hypertension, blood pressure 215/140; dyspnea; headache; occasional precordial pain
4	59	F	Hypertension, blood pressure 170/100; occasional severe dyspnea; heart enlarged to left
5	72	M	Hypertension, blood pressure 230/140; no cardiovascular symptoms
6	53	F	Hypertension, blood pressure 170/100; occasional precordial pain
7	33	F	Rheumatic heart disease; repeated decompensation and digitalization
8	52	M	Compensated mitral stenosis
9	66	M	Coronary occlusion; blood pressure 135/80; occasional precordial pain; dyspnea on exertion; controlled diabetes
10	62	M	Patient nervous; diagnosis not entirely clear; auricular fibrillation; old coronary occlusion
11	73	M	Chronic glomerulonephritis; left hydrothorax; edema of lower extremities; secondary cardiac decompensation
12	65	M	Moderate myocardial damage and premature ventricular contractions revealed by electrocardiogram; peculiar sound at area of mitral valve suggestive of ossification of valve
13	65	M	Edema of ankles and abdomen; dyspnea; fatigability; enlargement of heart to left; reduced renal function; auricular fibrillation and myocardial damage revealed by electrocardiogram
14	53	M	Mitral stenosis; symptoms of decompensation; attacks of unconsciousness
15	60	M	Hypertensive heart disease; tabetic form of dementia paralytica; blood pressure 220/130; heart enlarged to left; dyspnea on exertion
16	40	M	Pulmonary embolism 18 months ago; occasional dizziness; dyspnea on exertion; reduced working capacity; no objective cardiovascular findings
17	63	M	Coronary occlusion; severe pain in arms and hands; controlled diabetes
18	47	M	Myocardial damage revealed by electrocardiogram; no symptoms of decompensation; pain in left part of precordium
19	45	F	Hypertension, blood pressure 220/160
20	30	M	Hypertension, blood pressure 150/120; headache
21	54	M	Coronary sclerosis; bronchial asthma; possible myocardial damage revealed by electrocardiogram; dyspnea; palpitation; severe pain in left arm
22	70	M	Coronary arterial disease with pulmonary congestion; no angina
23	45	F	Hypertension, blood pressure 270/150, with palpitation and sometimes dizziness; digitalization

Normal subjects were found to have small daily variations. Hence a greater variation of the values in patients must be due to fluctuation in the state of the patients. Normal values decreased slightly with age. But this was true only for the statistical comparison of different age groups; single values overlapped. Thus, it was not necessary to take into consideration the ages of the patients in comparing their values with normal ones.

RESULTS

Since the values of the patients before the onset of disease are unknown, those determined in the present tests are classified in four categories, as follows: (1) decrease not probable, if the values are above the normal average; (2) decrease possible, if the values are between the normal average and the mean value of the normal average and the lowest normal limit; (3) decrease probable if the values are between

6. Footnote deleted by author.

the mean value and the lowest normal limit, and (4) pathologic decrease, if the values are below the lowest normal value. Only the fourth category is clearly defined; a pathologic decrease is proved if the patient's value is lower than the lowest of a sufficiently large number of normal subjects. All other categories are only approximate; a decrease, for instance, cannot be excluded even if the patient's value exceeds the normal average, but a decrease would not be probable in such a case.

Eight values were obtained by the repeated performance of the test: the maximum and minimum values for the right hand, first and second performances, and the corresponding values for two performances of the left hand. Table 1 shows the values of 42 normal subjects, the average, the lowest limit and the mean value determined by the

TABLE 1.—*Values of Motor Frequency (Impulses per Ten Seconds) of Forty-Two Normal Subjects*

Values	Right Hand				Left Hand			
	First Performance		Second Performance		First Performance		Second Performance	
	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum
Average (A).....	69.7	56.0	67.5	57.2	61.5	49.5	62.0	49.8
Lowest limit (L).....	60.0	45.0	55.0	40.0	55.0	40.0	50.0	39.0
Mean value (M).....	61.4	50.5	61.3	53.1	59.8	44.8	50.0	41.4
$\frac{A + L}{2}$								

formula $\frac{A + L}{2}$, in which A = the normal average and L = the lowest normal value.

According to these normal standards, we arranged the patients' values in the four categories (table 2). The normal average, mean and lowest values are indicated by double lines. The absolute average, mean and lowest values are different for each of the eight maximum and minimum values; they are indicated in table 1.

Table 2 shows the values of the patients; each patient is identified by his number in the synopsis. Few values are in the category "decrease not probable." Most of the eight maximum and minimum values are below normal average. The maximum frequency of motor impulses is undoubtedly diminished in hypertension and in heart disease.

Most values of the patients lie below the lowest limit of normal, in the category "pathologic decrease." This is significant, for it shows that the method is able to reveal individual deviations as well as the reaction of the patients as a group in a statistical comparison with

TABLE 2.—*Values of Motor Impulse Frequency in Twenty-Three Patients with Hypertension or Heart Disease*

Patient No.	Right Hand				Left Hand				Classification	
	First Performance		Second Performance		First Performance		Second Performance			
	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum		
1	75	65	Decrease not probable	
5	68	..	71	55	73	50		
7	70	56		
10	70		
11	50		
15	..	60	68	59	68	51	63	51		
16	50	Normal average	
20	78	..	75	63	..		
1	..	55	65	56	..	48	58	48		Decrease possible
2	67	..	62	..	61	..	61	47		
4	48		
5	68	55	..	56		
7	65	54	60	..	57	..		
8	..	51	62	47	..	47		
10	57	..		
11	60	..		
15	68		
16	..	52	61	..	58	48		
18	65	45		
19	45		
20	..	53	65	47		
Mean										
2	..	49	..	52	..	47	Decrease probable	
3	41	52	41		
4	63	..	59	44	55	..		
6	53	40		
7	44	..	43		
8	61	51	53	..	55	..		
9	..	45	50	..		
10	55	..	60	42	..	40		
11	..	47		
16	63	..	57	53		
17	40		
18	60	55	..		
19	..	41	43	52	..		
20	53	..	40		
22	39		
23	..	45	58	42	..	41		
Lowest limit of normal										
3	43	37	48	38	46	Pathologic decrease	
4	..	39	..	48	48		
6	57	42	49	34	49	30		
9	57	..	52	36	47	37	..	28		
10	..	41	..	24		
11	53	..	53	47	50	38		
12	52	41	47	37	43	33	40	32		
13	47	22	36	25		
14	57	41	48	41	48	33	48	37		
17	58	42	52	42	47	38	47	..		
18	..	40	..	33	41	31		
19	54	..	57	47	50		
21	48	42	40	37	38	32	39	35		
22	50	39	50	43	45	30	43	..		
23	58	..	50	37	47	..		

the reaction of normal persons as a group. Table 3 gives the average values and the lowest values of the 23 patients. The values of 4 patients with coronary occlusion are indicated as a separate group (patients 9, 17, 21 and 22).

The average values and the lowest values of the patients are considerably lower than those of the normal subjects (table 1).

The analysis of table 2 shows that the values of the patients shift into different categories for the different maximum and minimum values. Thus, for instance, for patient 17 all values but one are in the group "pathologic decrease"; the minimum value for the second performance of the left hand is in the group "probable decrease." Especially pronounced is the shifting of the values of patient 10; the initial value for the right hand is high, 70, and in the category "decrease not probable." During the first performance it falls to the minimum value of 41. Although the

TABLE 3.—Average and Lowest Values of Motor Impulse Frequency in Patients

Values	Right Hand				Left Hand			
	First Performance		Second Performance		First Performance		Second Performance	
	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum
Averages of values of all patients (23)	60.1	45.4	56.5*	44.5*	52.5	46.4	53.8*	42.8*
Lowest values.....	43	22	40	24	36	25	39	28
Averages of values of patients with coronary occlusion (4)	53.2	42.0	48.5	39.5	44.3	34.3	44.8	35.5

* The values of only 22 patients were used in calculating this average.

initial frequency seems to be normal in this case, the difference between maximum and minimum values is enormously increased, suggestive of a pathologically increased fatigability of the motor centers.

A pathologic deviation must be assumed even if one of the values of a patient (of a total of eight maximum and minimum values) is below the normal lowest limit (L). The more of the values lie in the category "pathologic decrease" and the lower the values, the more pronounced is the pathologic deviation.

We analyzed the number of maximum and minimum values which are in the category "pathologic decrease" for the different patients. As the total of maximum and minimum values amounts to eight, the highest possible number of pathologically decreased values is eight. The minimum possible number of decreased values is, of course, none. In this case all values would be higher than the lowest normal limit (L).

A similar analysis was performed with regard to the combined groups "pathologic decrease" and "probable decrease." The results are

given in table 4. In the first horizontal column the number of maximum and minimum values is indicated, beginning with zero. The second horizontal column concerns the number of patients that corresponds to the number of pathologically decreased values in the first column. The third horizontal column gives the number of patients with values in both categories, "pathologic decrease" and "probable decrease."

For 4 of our patients all eight maximum and minimum values were below the lowest limit. We included patient 13 in this category; he felt too tired to repeat his performance, so that we have obtained only the four values of the first performance. These were the lowest of all values.

For 10 of our patients five of the eight maximum and minimum values are in the zone "pathological decrease," and for 15 patients two values lie in this category. For 8 of the 23 patients all values exceed the lowest limit.

For 10 patients all eight values are lower than the M line, i. e., at least probably decreased. For 12 patients, seven of the eight values are

TABLE 4.—*Number of Patients (Twenty-Three) with Decrease in Eight or Less Maximum and Minimum Values*

Group	8	7	6	5	4	3	2	1	0
Pathologic decrease (below lowest limit of normal)	4	6	8	10	13	14	15	15	8
Pathologic decrease and probable decrease... (below mean value)	10	12	15	15	16	18	20	21	2

at least probably decreased, and for 2 patients of 23 all values are above the M line. This analysis shows that the functional state of the motor centers is pathologically decreased in about two thirds of all patients and probably decreased in about nine tenths of all patients. It may be mentioned that some of our patients had no symptoms of decompensation; for instance, patient 1 had fully compensated mitral stenosis.

In order to determine whether the results run parallel with the clinical findings and the actual state of the patients, we have taken for each of the eight maximum and minimum values the five highest and five lowest of our material. A complete correlation cannot be expected, since the deviation of central nervous functions may be different in different patients with similar clinical findings.

What we expect is a higher percentage of compensation in patients in the class with the highest values and a higher percentage of decompensation in patients in the class with the lowest values.

If the fifth value was equal for several patients, all of them were taken. Into this class of those with the five highest values fall 11 patients (1, 2, 4, 5, 7, 8, 10, 11, 15, 16 and 20). With the exception of patients 15, 7 and 4 all of them were without, or with only slight symptoms of,

decompensation. One value of patient 4, who had symptoms of decompensation, falls into the group "decrease possible." But three values of the same patient are in the group "pathologic decrease."

The highest initial values for the right hand are found for patient 20 (78), patient 1 (75) and patients 7 and 10 (70). This frequency drops to 55 for patients 1 and 20 and to 41 for patient 10. In all of these patients the fatigability of motor centers seems to be increased.

In the same way, we analyzed which patients belong to the class with the five lowest values in the eight maximum and minimum values. We found patients 3, 4, 6, 9, 10, 11, 12, 13, 14, 17, 18, 19, 21, 22 and 23 were in this class. Of these 15 patients, 9 had symptoms of decompensation. In 4 of the remaining 6, some additional factors may be responsible for the decrease of motor frequency, for instance, in patients 8 and 6 pain in the arms and chest and in patient 11 renal insufficiency. The low value of patient 10 seems to be partially of nervous origin.

Taken all in all, most of the patients whose values are found to be among the five lowest showed symptoms of decompensation, whereas most patients in the class with the five highest values did not. Hence, there seems to be a parallelism between the frequency of motor impulses and the state of the patient.

The 4 patients with coronary occlusion are among those with the five lowest values. For these patients, six maximum and minimum values are below the lowest limit, and two are below the M line (patient 9); patients 17 and 22 have seven values in the category "pathologic decrease" and one in the category "probable decrease"; all the values of patient 21 lie in the category "pathologic decrease." Thus the results are uniform and consistent in these instances of coronary occlusion. The averages of the values of the patients with coronary occlusion are much lower than those of the other patients (table 3).

The drop of the motor frequency during the test was found to be dependent on the absolute initial value in the normal subjects; the higher the maximum, the more pronounced was the decrease.

We found a positive correlation between the drop of frequency and the maximum value for patients, especially with regard to group correlation, by dividing our material in five series of 4 patients and a sixth series of 3 patients. This separation is justified, because the daily variations may amount to ± 2 impulses. A classification into groups reduces the effect of daily variations to a certain extent. The correlation coefficients, calculated according to Spearman's formula, ranged between 0.97 and 0.99 for both hands and both performances. These high coefficients indicate a close relation between initial value and the drop of frequency. In figure 1 the increase of the drop of frequency (ordinate) with the increase of the maximum frequency (abscissa) is plotted for the first performance, right hand, in a broken line for the normal sub-

jects and in a full line for the patients (mean values of six groups). Both lines run parallel, but that of the patients is considerably higher. This is clear evidence that the fatigability of the motor centers in the patients is appreciably greater than it is in the normal subjects.

In normal subjects, the maximum frequency was almost always identical with the initial value. In 3 subjects (7.1 per cent) of a total of 42 the maximum frequency was reached after the first ten seconds.

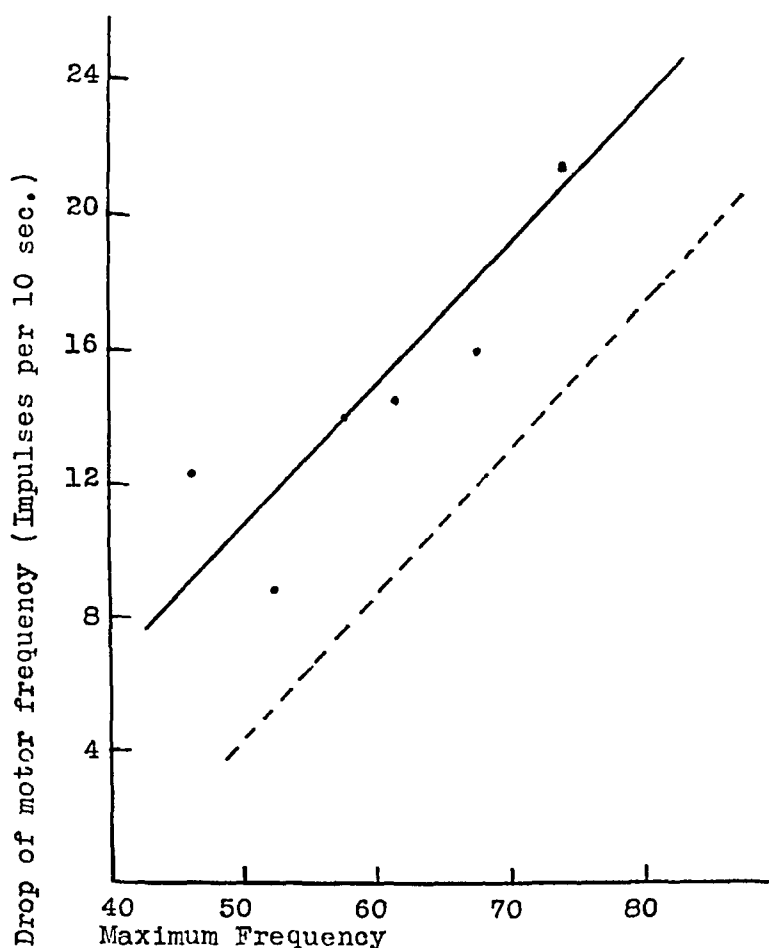


Fig. 1.—Drop in the frequency of motor impulses dependent on the maximum frequency of impulses. The broken line indicates the values for a group of 42 normal subjects, and the unbroken one signifies the values for a group of 23 patients with hypertension or heart disease.

Since in each experiment four performances were tested, a dissociation between the initial value and the maximum frequency was observed in only 3 (1.78 per cent) of 168 test performances of normal subjects. In the patients, the maximum frequency was reached after the first ten seconds in 10 of 23 patients (3, 4, 6, 8, 9, 11, 14, 18, 21 and 22), that is, almost half (43.5 per cent) the total number of patients, or in

15 (16.17 per cent) of a total of 90 performances. Nine of these 10 patients belong to the class with the five lowest values.

The dissociation of initial and maximum frequency which is rare in normal subjects is much more frequently observed in patients. If one takes only patients with symptoms of decompensation, the proportion increases still more; most of these patients reach, in one of the performances at least, the maximum frequency after the first ten seconds, usually between the tenth and the thirtieth seconds. The shape of the

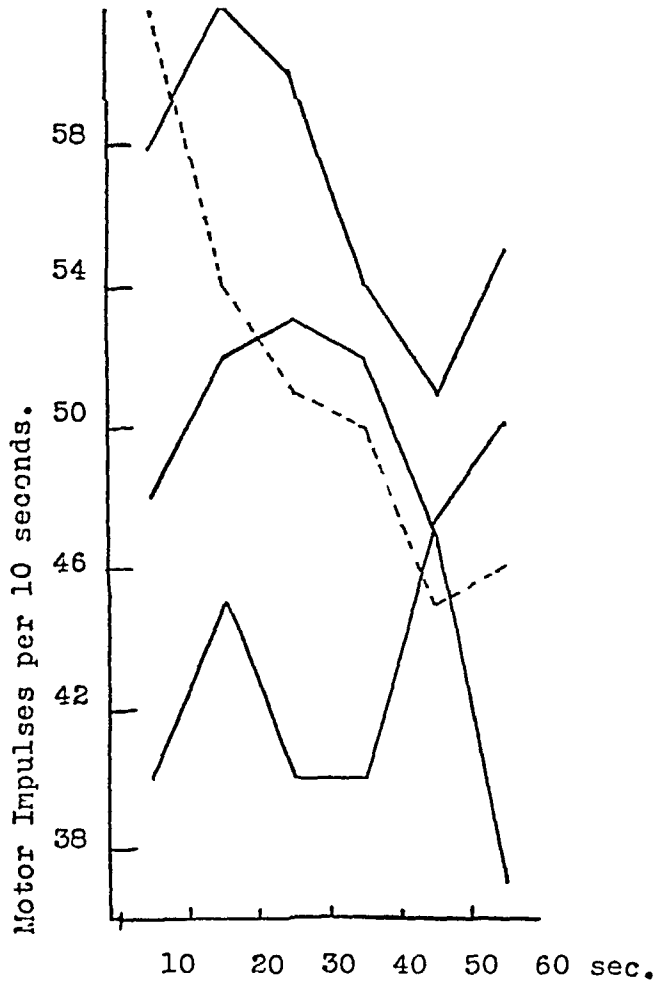


Fig. 2.—Drop in the frequency of motor impulses during a sixty second performance. The broken line indicates the values for a normal subject, and the unbroken lines signify the values for 3 patients with hypertension or heart disease.

curves is greatly altered. Figure 2 shows curves of 3 patients (solid line) compared with a typical normal curve (broken line); the frequency is plotted on the ordinate and the time on the abscissa.

The increase of the impulse frequency during the first ten to thirty seconds is undoubtedly due to adaptation processes. We must assume that the motor centers (and perhaps other centers too) are in a low functional state in these patients during rest. The centers are apt to

develop only a low frequency of impulses. This low excitatory state improves during the performance. The improvement cannot be due to improvement of circulation, ten to thirty seconds being much too short a time for circulatory processes to be effective. The adaptation processes leading to the improvement of the functional state of motor centers must be of nervous origin. Thus, adaptation is not lost in these patients, and even may be enhanced by the low initial functional state. Further observation will reveal whether this is a favorable sign or not.

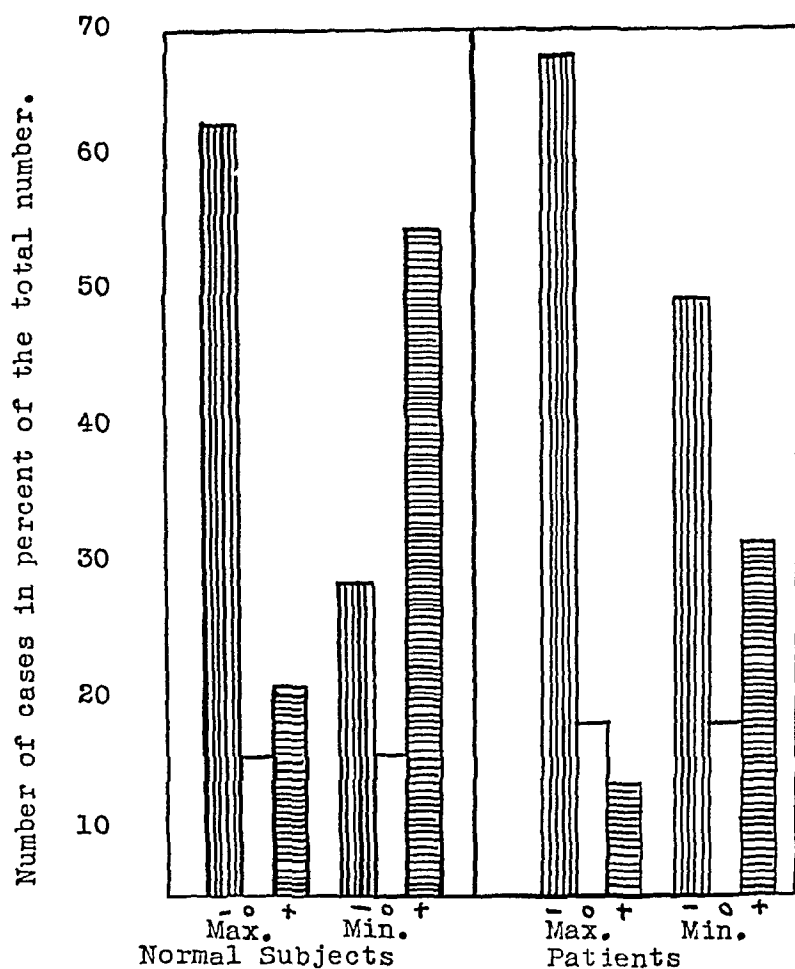


Fig. 3.—The number (in percentage) of normal subjects and patients with hypertension or heart disease with increase (+) or decrease (—) of maximum and minimum values of frequency of motor impulses in the second performance compared with the values of the first performance.

The comparison of the first and the second performance does not give a quantitative expression of fatigue or of adaptation, but it does show whether fatigue or adaptation prevails during the second performance as a result of the antecedent performance. The comparison of the values of the first and of the second performance in the normal subjects revealed an influence of both fatigue and adaptation: As a

result of fatigue, the maximum frequency was lower in the second performance, but, as a result of adaptation, the frequency did not drop as much as in the first performance, so that the minimum value was higher and the second performance as a whole was better stabilized. In order to compare the values of normal subjects and of patients by the same scale, we calculated all values in percentage. Figure 3 shows the result for the right hand. The columns indicate the number of patients in percentage of the total number of subjects. The number of persons with equal values in the first and the second performance is constant for the maximum and minimum values and is 15.8 per cent for the normal subjects and 18.2 per cent for the patients. In the maximum values of the normal subjects the number of instances of negative differences (lower in the second performance) is three times the number of positive differences (higher in the second performance); but in the minimum values the number of positive differences is about twice the number of negative differences. Thus, in the normal subjects the differences shifted from minus to plus when the maximum and minimum values were compared. In the patients, this shift did not occur.

In the patients, the number of negative differences of the maximum values is five times the number of positive differences. In the minimum values, the number of negative differences still exceeds the number of positive differences about one and five-tenths times.

The comparison of the values of the left hand between normal subjects and patients reveals a tendency similar to those of the right hand, although not so distinct. This variation is due to the fact that the maximum values of the left hand are more decreased in patients than in normal subjects, so that the drop of frequency during the performance—as dependent on the absolute value of the maximum frequency—becomes less. The comparison of values for the first and the second performance reveals a much greater prevailing fatigue in patients as an after-effect of the first performance than could be observed in normal subjects. The shape of the curves has revealed the existence of adaptation processes in patients (fig. 2) but their importance is reduced by the overwhelming influence of fatigue.

COMMENT

The maximum frequency of motor impulses is generally decreased in circulatory insufficiency. This result is similar to the decrease of the fusion frequency of flicker as described in a previous paper by an associate and us.¹ The results of these investigations broaden the base of our opinion that circulatory insufficiency leads to a deterioration of central nervous functions, which change seems to be important for the

increased fatigability of patients not only during physical but during mental work and even during rest.

The difference between the normal values and those of patients for maximum frequency of motor impulses is not so distinct as it is for the fusion frequency of flicker. Nevertheless, in 15 of 23 patients at least one maximum or minimum of a possible total of eight values was lower than the lowest normal value. This shows that the four performances the subject has to carry out reveal more deviations than only the measurement of the initial value would do.

The more distinct differences between normal subjects and patients in the fusion frequency of flicker confirm our expectations (see introductory paragraphs). The correlation coefficients between the fusion frequency of flicker and the maximum frequency of the first performances of both hands were calculated. Only the patients with normal vision were taken for this calculation. We found no correlation. It

TABLE 5.—*Influence of the Patient's Condition on the Motor Impulse Frequency*

Patient No.	Examination	Right Hand				Left Hand			
		First Performance		Second Performance		First Performance		Second Performance	
		Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
2	1	67	49	62	52	61	47	61	47
	2	65	48	57	45	58	46	55	41
21	1	48	42	40	37	38	32	39	35
	2	43	31	35	28	30	21	32	23

may be mentioned that in normal subjects there is no correlation between the fusion frequency and the frequency of motor impulses. It is interesting that such a general influence as circulatory insufficiency affects sensory and motor centers differently. Therefore, the combined application of both methods seems to be advisable.

We mentioned that as a rule the frequency of motor impulses does conform with the state of the patients. This generalization is based on results obtained by comparison of different patients. This conclusion could be confirmed by repeated investigations of the patient under different conditions. We had the opportunity to do so in 2 patients (2 and 21). The first was a patient with compensated mitral stenosis complicated by pregnancy. The first examination was performed in the fourth month of pregnancy and the second in the seventh month. All data were lower in the second examination, especially the values in the second performance, which change indicated an increased fatigability (table 5).

Patient 21 came into the hospital a week after the first examination in a much worse condition. He had suffered from severe pains during

the whole night. The values of the second examination were much lower than those of the first (table 5).

The principal reason for the decrease of the frequency of motor impulses in hypertension or heart disease must be the lack of oxygen supply to the central nervous system. The literature on this question, so far as the more general problems are concerned, has been discussed in a preceding paper.¹ Many investigations have been performed with muscular exercise at low oxygen tension, and all authors agree that the working capacity is decreased in these conditions. In most of these investigations types of work have been used in which peripheral physiologic functions are involved, so they do not indicate necessarily a decreased function of the motor centers. Much more significant for our problem is the disturbance of the finer coordinating abilities, for instance, disturbance of handwriting. The process of writing is soon influenced by reduced oxygen tension, and if the oxygen deficiency increases it is rapidly impaired.⁷ In the handwriting test, just as in our method peripheral functions do not play any considerable role. But the handwriting test, as a coordination test, concerns the association of different centers.

Although the principal reason for the deterioration of the motor centers is the lack of oxygen in them, we held it possible that pain may play a contributing role. The values of our 4 patients with coronary occlusion are consistently in the group "pathologic decrease," and so are those of patients 3 and 6, with hypertension and pain in the chest.

It seems possible that afferent pain impulses (the origin of the pain seems to be a symptom of deficient oxygen supply in the muscles, according to Katz and associates⁸) spread through the central nervous system and affect the motor centers. The experiments of Forbes and Morrison⁹ are strong evidence for this possibility. They observed in anesthetized cats a primary and, after a latent period of one second, a secondary discharge after electric stimulation of the sciatic nerve by induction shocks. Whereas the primary discharge is localized, the secondary discharge is widespread in the cerebral center. Thus, the secondary discharge would reach the motor centers and might, as a subliminal stimulation, alter their state without provoking a direct motor action. There are numerous examples in the physiologic behavior of

7. Jokl, E.: Some Modern Problems of Aviation Medicine, read at the Thirty-Second Annual Meeting of the South African Medical Congress, September 1938.

8. Katz, L. N.; Lindner, E., and Landt, H.: On the Nature of the Substance Producing Pain in Contracting Skeletal Muscle: Its Bearing on the Problems of Angina Pectoris and Intermittent Claudication, *J. Clin. Investigation* **14**:807, 1935.

9. Forbes, A., and Morrison, B. R.: Cortical Response to Sensory Stimulation Under Deep Barbiturate Narcosis, *J. Neurophysiol.* **2**:112, 1939.

the central nervous system of the effect of subliminal stimulation. In connection with this Michailov's¹⁰ results are important in that he obtained an increase of the motor chronaxia after different pain stimuli. Possibly these results are the bridge between our findings and the results of the experiments of Forbes and Morrison. For the present, however, we do not regard the additional influence of pain as an established fact.

The results of this and of the previous paper show that disturbance of central nervous processes may be as early a symptom of circulatory insufficiency as the hitherto preferably studied symptom of peripheral decompensation.

SUMMARY

1. The maximum frequency of motor impulses is reduced in circulatory insufficiency.

2. The decrease of the frequency of motor impulses generally conforms to the gravity of the symptoms of decompensation.

3. The fatigability of motor centers in patients with hypertension or heart disease is increased.

4. The shape of frequency fatigue curves is often altered in patients with such a condition.

5. Although there is evidence that adaptation processes are not abolished in such patients, fatigue detectable in the subsequent performance prevails in them as an after-effect of the precedent test, whereas in normal subjects the influence of adaptation diminishes the fatigue in the subsequent performance.

6. The principal reason for the deterioration of motor centers is assumed to be the lack of oxygen in the central nervous system.

10. Michailov, V. D.: Les déformations de la chronaxie et de la rhéobose du muscle strié sous l'influence des différentes irritations douloureuses, *Bull. biol. et méd. expér. URSS* 6:504, 1938.

ACACIA IN TREATMENT OF THE NEPHROTIC SYNDROME

WITH SPECIAL REFERENCE TO EXCRETION OF CHLORIDE AND
WATER; A REPORT OF CASES

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Elsewhere ¹ two of us (A. G. and M. W. B.) have summarized our clinical experience with acacia in the treatment of nephrotic edema. In a consecutive series of 40 patients it was found that 36, or 90 per cent, could be relieved of edema when they followed a regimen of diet, ingestion of potassium nitrate and injections of acacia.

The reason acacia originally was administered is obvious. It was thought that injections of solutions of this colloid material would increase the colloid osmotic pressure of the serum in cases of nephrotic edema and thus facilitate the reabsorption of the fluid resulting from edema. However, actual determination of colloid osmotic pressure before and after a therapeutic course of injections of acacia did not reveal consistent differences. Goudsmit, Binger and Power ² found that after completion of a course of injections of acacia the colloid osmotic pressure in 43 per cent of a series of 28 patients was definitely increased. In the remaining 57 per cent it was unchanged or decreased, a definite decrease being observed in 18 per cent. There seemed to be little correlation between diuretic response and changes in colloid osmotic pressure. In 4 cases in which definite decreases of colloid osmotic pressure were observed, the therapeutic response was as satisfactory as in 9 cases in which the colloid osmotic pressure increased subsequent to the administration of acacia.

In cases of the nephrotic syndrome the most outstanding deficiency of renal excretion relates to the inability of the patient to eliminate all

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* At the time this work was done Dr. Goudsmit was a Fellow in Medicine of the Mayo Foundation.

1. Goudsmit, A., Jr., and Binger, M. W.: Acacia in the Treatment of the Nephrotic Syndrome, *Arch. Int. Med.* **66**:1252-1281 (Dec.) 1940.

2. Goudsmit, A., Jr.; Binger, M. W., and Power, M. H.: Unpublished data.

sodium chloride and water ingested during twenty-four hours. The retention and subsequent accumulation of these substances in the lymph and tissue spaces are responsible for the appearance of edema, without which the nephrotic syndrome is usually clinically asymptomatic. In view of the absence of correlation between changes in colloid osmotic pressure and therapeutic effect of injections of acacia, the possibility of acacia's facilitating the excretion of chloride by the kidney thus had to be considered. Experiments on healthy dogs undertaken by Goudsmit, Power and Bollman³ to investigate this problem showed that the excretion of chloride subsequent to an injection of acacia increased between 4 and 352 per cent, with an average of 189 per cent. This increase was independent of changes in urinary volume and appeared all the more significant because usually, as a consequence of dilution with solution of acacia, the concentration of chloride in the plasma was diminished. The clearances of creatinine and of urea were essentially unchanged.

In view of these results obtained in experiments on dogs, it was decided to extend the study to the investigation of excretion of chlorides by patients who had the nephrotic syndrome. The present study incorporates data on 5 such patients, 4 treated with acacia and 1 treated by means of diet and potassium nitrate, without the use of acacia.

METHODS

Diagnostic criteria, as well as the general regimen of treatment with diet, potassium nitrate and acacia, have been more fully discussed elsewhere.¹ All patients were hospitalized and received a standard low salt (so-called salt-free), high protein diet. Intake of fluids by mouth was restricted and carefully checked. The patients were weighed every morning before breakfast. Urine was collected over twenty-four hour periods starting at 7 a. m. one day and ending at 7 a. m. the next day. For convenience, in the charts presented herein such twenty-four hour periods have been designated as days.

As is well known, diets termed salt free contain small amounts of sodium chloride. Repeated analyses of salt-free, high protein diets served in the hospitals of our city in amounts containing approximately 2,000 calories per twenty-four hours have shown contents of sodium chloride varying between 1 and 2 Gm. Since this amount of sodium chloride is similar to that excreted in feces and perspiration over a period of twenty-four hours, for experiments of relatively short duration, such as are presented herein, the amount of chloride excreted in the urine may be considered to be the net loss of chloride. The additive net loss of chloride from period to period thus represents cumulative chloride loss.

The acacia used in this study was a 6 per cent solution in distilled water, prepared for us by a commercial laboratory.

3. Goudsmit, A., Jr.; Power, M. H., and Bollman, J. L.: Some Effects of the Injection of Acacia with Special Reference to Renal Function, *Proc. Soc. Exper. Biol. & Med.* **47**:254-257 (June) 1941.

Urinalysis, determinations of blood urea according to Van Slyke and Cullen, of chloride in the urine according to Wilson and Ball, of plasma chloride according to Osterberg and Schmidt, of carbon dioxide-combining power according to Hawk and Bergheim and of blood urea clearance, concentration of cholesterol in the blood, concentration of the serum proteins and the albumin-globulin ratio were carried out according to the directions of Todd and Sanford.⁴ The colloid osmotic pressure of the serum was determined according to the method of Butt, Power and Keys,⁵ reported in an article that also contains a description of Power's method for determination of concentration of acacia in serum, which was employed in the present study.

In the charts contained here, the excretion of 5 Gm. of sodium chloride, calculated from the equivalent excretion of chloride, has been represented by a block as high as one representing 1,000 cc. of urine. A loss in weight of 1 Kg. and a cumulative loss of sodium chloride amounting to 5 Gm. have been plotted on an equal scale.

REPORT OF CASES

CASE 1.—A 29 year old woman having chronic glomerulonephritis with marked nephrotic features was first admitted to the hospital in 1937, at which time acacia was used successfully.⁶ She returned to her home and remained free of edema. Thirteen months after her dismissal from the hospital, when she came back for reexamination, no edema was noted. Albuminuria, graded 4, persisted, but her condition otherwise appeared satisfactory. The patient was directed to continue her regular regimen.

Shortly afterward, because of a change in circumstances, this patient had to start to work to earn her living. From that time on swelling reappeared and increased gradually during the following four months.

On the patient's readmission to the hospital, moderate edema of the feet, legs and lumbosacral region was found. The blood pressure was normal, as were the ocular fundi. Urinalysis showed a specific gravity of 1.032, albumin graded 3, casts graded 1, and occasional erythrocytes. The blood per hundred cubic centimeters contained 26 mg. of urea, 641 mg. of cholesterol and 633 mg. of chloride (expressed as sodium chloride). The carbon dioxide-combining power was 48.5 volumes per cent. The serum per hundred cubic centimeters contained 47 mg. of acacia and 3.8 Gm. of protein. The albumin-globulin ratio was 1:1.1. The clearance of urea amounted to 20.1 cc. per minute at a volume of 10 cc. per hour.

This patient's course in the hospital is illustrated in figure 1. As can be seen, before special therapy was instituted the urinary volume amounted to 350 to 400 cc. each twenty-four hours; the excretion of chloride was 1.1 Gm. On the third day, 500 cc. of a 6 per cent solution of acacia was administered in the morning and 500 cc. early in the evening. The urinary volume that day rose to 2,800 cc. and the excretion of sodium chloride to 17.2 Gm. During the next four days

4. Todd, J. C., and Sanford, A. H.: *Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology*, ed. 9, Philadelphia, W. B. Saunders Company, 1939.

5. Butt, H. R.; Power, M. H., and Keys, A.: The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, *J. Lab. & Clin. Med.* **24**:690-695 (April) 1939.

6. The course of this patient's disease in 1937 has been reported by Goudsmit and Binger (case 1).¹

the excretion of sodium chloride continued to be considerably above the control value, and after one more injection of 500 cc. of a 6 per cent solution of acacia the patient had lost a total of 48 Gm. of sodium chloride and 3.2 Kg. (7 pounds) of weight. At that time, to reenforce the effect of acacia, administration of potassium nitrate orally was started. This procedure led to additional loss of weight, as well as of chloride. The intravenous administration of 1 cc. of esidrone (the sodium salt of pyridinedicarboxy- β -mercuri- ω -hydroxypropylamide-theophylline) was followed by only a slight increase in excretion of sodium chloride and of water, and on the fourteenth day the patient was dismissed from the hospital, having lost 74 Gm. of sodium chloride and 4.7 Kg. (10.3 pounds) of weight, with, as noted by the physician, "perhaps just a trace of lumbar edema." Three days after dismissal, the patient's serum proteins were 2.8 Gm. per hundred cubic centimeters, the albumin-globulin ratio was 1.1:1 and the concentration of acacia in the serum was 1,950 mg. per hundred cubic centimeters. One day before

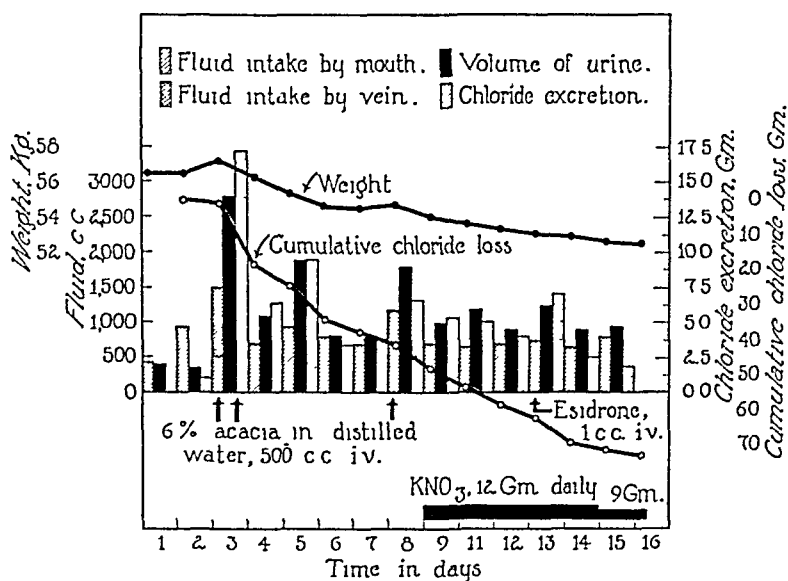


Fig. 1.—Excretion of water and of chlorides by a patient (case 1) who had nephrotic edema, treated with intravenous injections of acacia and with potassium nitrate given by mouth. Daily diet: protein, 75 Gm.; calories, 1,800; salt, none; fluids by mouth, 800 cc. Esidrone is the sodium salt of pyridinedicarboxy- β -mercuri- ω -hydroxypropylamide-theophylline.

dismissal the blood plasma per hundred cubic centimeters contained 521 mg. of cholesterol and 575 mg. of chloride (expressed as sodium chloride) per hundred cubic centimeters.

In view of the occurrences attendant on this case, it is obvious that the administration of acacia was followed by a most striking increase in the excretion of water and of sodium chloride. On a number of occasions after the administration of acacia, the concentration of sodium chloride in the twenty-four hour specimen of urine was more than 0.5 per cent. After the administration of esidrone, the increase in excretion of water and of sodium chloride remained considerably below the amounts excreted after the administration of acacia alone.

CASE 2.—A 19 year old unmarried woman was admitted to the clinic on Nov. 28, 1938. She stated that she had been suffering from swelling around the eyes for the previous three years. A year and a half previously her ankles had begun to be slightly swollen, and a year previously, although she had remissions, her condition gradually had become worse.

On examination the patient's face was found to be slightly puffy. Considerable edema of the sacral and the lumbar regions and of the legs and ankles was found. She had ascites, graded 2, and fluid in the left side of the thorax could be demonstrated on physical examination; the latter observation was confirmed by roentgenologic examination. The blood pressure was normal, and results of examination of the ocular fundi were essentially irrelevant. Urinalysis revealed a specific gravity of 1.027, albumin graded 4, casts graded 3, an occasional erythrocyte and pus graded 2. The blood per hundred cubic centimeters contained 42 mg.

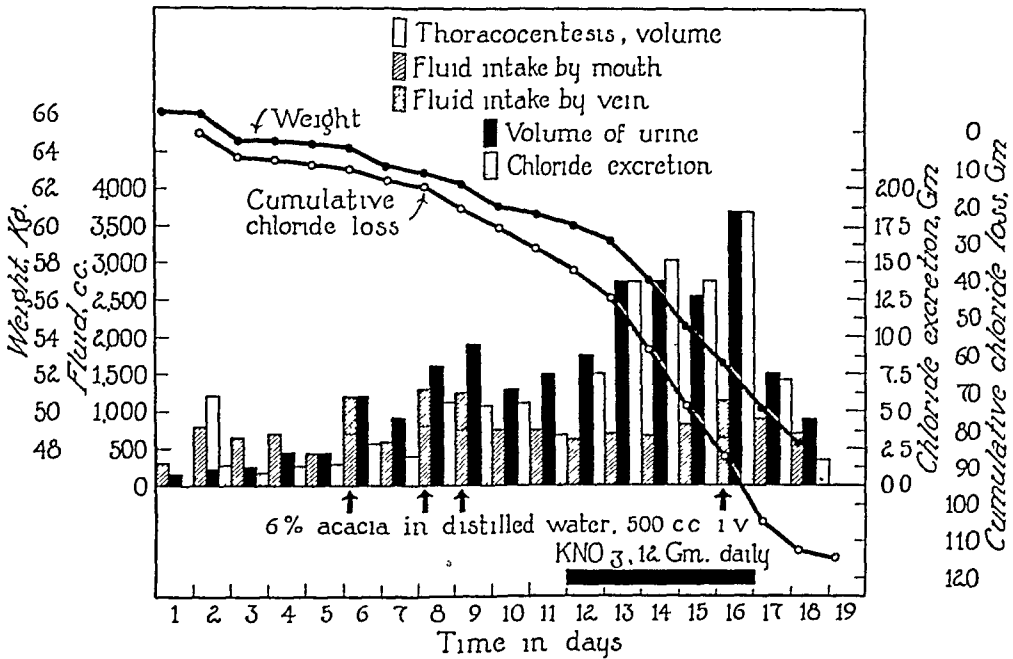


Fig. 2.—Excretion of water and of chlorides by a patient (case 2) who had nephrotic edema, treated with intravenous injections of acacia and with potassium nitrate given by mouth. Daily diet: protein, 80 Gm.; calories, 1,800; salt, none; fluids by mouth, 800 cc.

of urea and 641 mg. of cholesterol. The concentration of serum proteins was 2.8 Gm. per hundred cubic centimeters, and the albumin-globulin ratio was 2.1:1. A diagnosis of chronic glomerulonephritis with marked nephrotic features was made.

The patient's course in the hospital is illustrated in figure 2. On the second day thoracocentesis was performed, and 1,000 cc. of clear fluid was removed. The protein content of this fluid was 0.2 per cent, and the specific gravity was 1.011. The concomitant loss of sodium chloride, for the purposes of charting, was estimated at 5 Gm. The volume of urine for twenty-four hours varied between 150 and 450 cc., and excretion of sodium chloride for a similar period, between 0.8 and 1.5 Gm. On the day of the first injection of acacia a considerable increase in urinary volume, as well as in excretion of chloride, was seen, and after two

more injections the urinary volume increased to 1,900 cc. and the excretion of chloride to 5.3 Gm. per twenty-four hours. Thus, by the morning of the twelfth day this patient had lost a total of 37 Gm. of sodium chloride and 6.1 Kg. (13.4 pounds) of weight, of which the loss of 5 Gm. and of 1 Kg. respectively was caused by the mechanical removal of the fluid from the thorax. At this time the concentration of acacia was 1,800 mg. per hundred cubic centimeters of serum.

As a consequence of the administration of potassium nitrate, the urinary volume, as well as the excretion of chloride in the urine, was increased considerably. For a period of three days the excretion of water and of sodium chloride was essentially unchanged. When one more injection of acacia was administered, on the sixteenth day, the urinary volume increased to 3,700 cc. per twenty-four hours, which is nearly 1,000 cc. more than the volume during treatment with potassium nitrate alone. The amount of chloride excreted was 18.3 Gm., which is also in excess of that excreted on any one of the three previous days. As a consequence of these procedures, the patient rapidly lost weight, and on December 16 it was noted that there remained "just a trace of edema below the left elbow, no actual clinical edema elsewhere." One day after the last injection of acacia its concentration in the serum was 1,990 mg. per hundred cubic centimeters.

During her stay in the hospital, the patient lost a total of 16.8 Kg. (37.0 pounds) of weight and 114 Gm. of sodium chloride.

It would seem that in this case the concentration of sodium chloride in the twenty-four hour specimen of urine was essentially unchanged by the administration of acacia or potassium nitrate or the combination of the two. However, the absolute quantities excreted per twenty-four hours were considerably increased after the treatment was instituted. It is noteworthy that the first injection of acacia was not successful in producing a prolonged increase in the excretion of chloride and of water. However, after the second and third injections the increased excretion of chloride and of water appeared well maintained.

CASE 3.—The history of this patient has been reported elsewhere¹ (case 5). It might be summarized as follows: On a previous occasion a diagnosis of chronic glomerulonephritis with nephrotic features had been made, and the patient had been treated in the hospital with restriction of diet, potassium nitrate and injections of acacia. He had been dismissed free of edema and had been advised to continue the diet and the oral ingestion of potassium nitrate. He had remained free of edema until, after a gastrointestinal upset, he had discontinued ingestion of the potassium nitrate. After this, the swelling had recurred.

On the patient's readmission, urinalysis showed a specific gravity of 1.025, albumin graded 3, casts graded 3, occasional erythrocytes and pus graded 1. The blood per hundred cubic centimeters contained 22 mg. of urea, 490 mg. of cholesterol, 633 mg. of chloride (expressed as sodium chloride) and 3.1 Gm. of serum proteins. The carbon dioxide-combining power was 57 volumes per cent. The albumin-globulin ratio was 1.1:1, and the serum contained 225 mg. of acacia per hundred cubic centimeters. The colloid osmotic pressure of the serum was 95 mm. of water. The patient's course in the hospital is illustrated in figure 3. The response to injections of acacia, an increase in the concentration of this substance

in the serum after the third injection to 1,770 mg. per hundred cubic centimeters, was striking. The urinary volume increased to 2,500 cc. per twenty-four hours, and the excretion of sodium chloride in one day was as high as 14.1 Gm. The patient lost weight rapidly, so that on the day that the administration of potassium chloride was started his weight was 1 Kg. (about 2 pounds) more than it had been at the time of his previous dismissal from the hospital, when he was adjudged to be free of edema. He had lost 55 Gm. of sodium chloride and 6 Kg. (about 14 pounds) of weight. Despite the administration of potassium chloride, the chloride balance continued to be definitely negative. After a fourth injection of acacia in distilled water (which increased its concentration in the serum to 2,015 mg. per hundred cubic centimeters), 9.3 Gm. more of sodium chloride was lost. At the time of dismissal from the hospital, this patient's loss of weight amounted to 7 Kg. (approximately 15.4 pounds) and the loss of sodium chloride to 77 Gm.

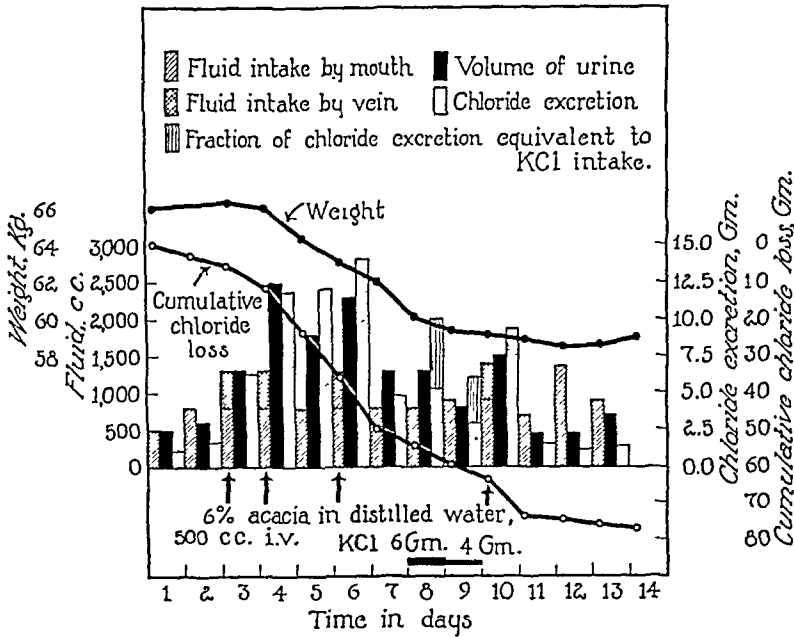


Fig. 3.—Excretion of water and of chlorides by a patient (case 3) who had nephrotic edema, treated with intravenous injections of acacia and with potassium chloride given by mouth. In the calculation of the “cumulative chloride loss” the equivalent in sodium chloride of the potassium chloride administered is considered as extra intake. Daily diet: protein, 80 Gm. (from the ninth day on: protein, 100 Gm.) ; calories, 2,000; salt, none; fluids by mouth, 800 cc.

In the report just presented it can be observed that the response of the excretion of water and of chloride following the injection of acacia was again definite. The concentration of chloride in the urine, which on the first two days of hospitalization was approximately 0.25 per cent, on many occasions increased to considerably more than 0.5 per cent subsequent to the administration of acacia. Potassium chloride, which was administered for only two days, with a total dose of 10 Gm., did not appreciably influence the course of the patient in the hospital. It is

obvious that after its administration a concentration of chloride in the urine, expressed as sodium chloride, was reached which was definitely more than the concentrations observed under other circumstances.

CASE 4.—A 69 year old man stated that four weeks previous to admission to the hospital he had noticed swelling of his abdomen, followed by swelling of his feet and legs and later of his face and hands. On this patient's admission, edema of the abdominal wall, graded 1 to 2, was found, as well as ascites, graded 1 to 2, and edema of the lumbosacral region and the legs and ankles, graded 2. The systolic blood pressure was 170 and the diastolic pressure was 90, expressed in millimeters of mercury; peripheral sclerosis, graded 2, was noted. Examination of the ocular fundi revealed the arterioles to be somewhat narrowed, with sclerosis, graded 1, of the chronic hypertensive type. Urinalysis showed a specific gravity

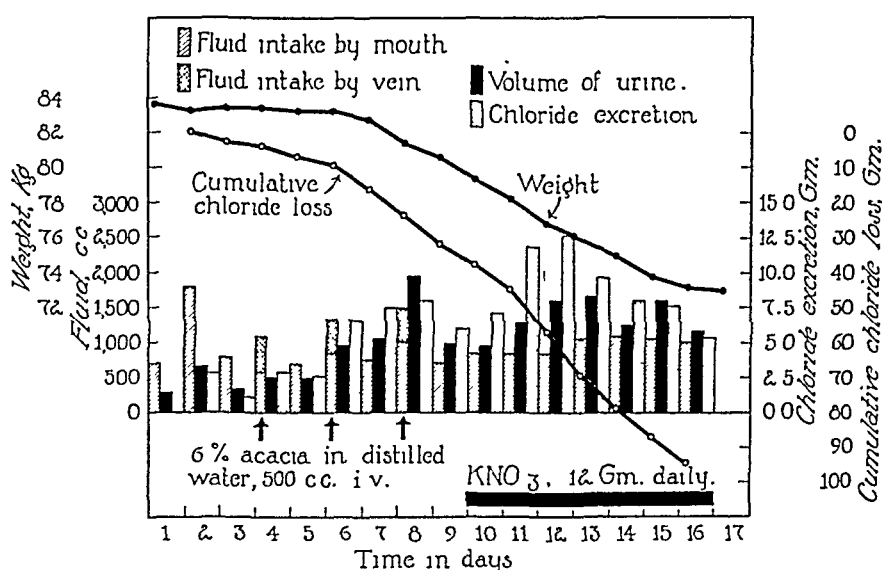


Fig. 4.—Excretion of water and of chlorides by a patient (case 4) who had nephrotic edema, treated with intravenous injections of acacia and with potassium nitrate given by mouth. Daily diet: protein, 70 Gm.; calories, 1,800; salt, none; fluids by mouth, 800 cc.

of 1.033, albumin graded 4, casts graded 3, an occasional erythrocyte and pus graded 1. The blood per hundred cubic centimeters contained 30 mg. of urea, 438 mg. of cholesterol, 561 mg. of chloride (expressed as sodium chloride) and 4.5 Gm. of serum proteins. The carbon dioxide-combining power was 54.1 volumes per cent. The albumin-globulin ratio was 1.2:1, and the clearance of urea was 65.2 cc. per minute, with a volume of 50 cc. per hour. A diagnosis of chronic glomerulonephritis with nephrotic features was made.

Features of the water and the chloride balance during the period of hospitalization are illustrated in figure 4. Three injections of acacia (bringing the concentration of this substance in the serum to 1,380 mg. per hundred cubic centimeters) on alternate days increased excretion of water and of chloride, so that on the morning of the day that administration of potassium nitrate was begun the patient

had lost 32 Gm. of sodium chloride and 4.3 Kg. (9.5 pounds) of weight. A definite diuretic response was obtained after the use of potassium nitrate, but the volume of urine never became as large as it had been on the day of the third injection of acacia. However, the excretion of chloride was considerably augmented. One day before dismissal the patient was entirely free of edema; he had lost 10.4 Kg. (22.9 pounds) of weight and 94 Gm. of sodium chloride. At the time of dismissal from the hospital, the blood per hundred cubic centimeters contained 44 mg. of urea, 309 mg. of cholesterol and 540 mg. of chloride (expressed as sodium chloride). The carbon dioxide-combining power was 61.7 volumes per cent.

Prior to the administration of acacia, the concentration of chloride in a twenty-four hour specimen of urine was approximately 0.5 per cent. After the injections, however, the concentration on nearly every day was maintained above this figure. On one day it was nearly 0.8 per cent. This relative excess in excretion of chloride over excretion of water was still further accentuated by the administration of potassium nitrate. Reinforcement of the diuretic measures with potassium nitrate in this case appeared to increase the rate of loss of chloride slightly more than it affected the rate of loss of weight. The concentration of chloride in the blood at the conclusion of the administration of potassium nitrate was essentially the same as it had been at the beginning.

CASE 5.—A 36 year old man was admitted to the clinic on Dec. 17, 1938. He stated that he had noted slight fatigue during the previous two months. One month before admission he had become aware of increased swelling of the feet, legs, arms and face. Erythrocytes and considerable albumin had been found in the urine, and he had gone to bed. Since that time his urinary volume had increased to approximately 2 quarts (1,892 cc.) daily, and he had lost 8 to 10 pounds (3.6 to 4.5 Kg.) of weight. Examination revealed edema, graded 2, of the sacral region, abdominal wall, ankles and legs. Peripheral sclerosis, graded 2, was noted. The systolic blood pressure was 168 and the diastolic pressure 110, expressed in millimeters of mercury. Examination of the ocular fundi revealed nothing abnormal except for a few hemorrhages, which the examining ophthalmologist interpreted as probably associated with anemia rather than with hypertension. Urinalysis showed a specific gravity of 1.015, albumin graded 4, casts graded 3, erythrocytes graded 4 and leukocytes graded 1. The blood per hundred cubic centimeters contained 10.8 Gm. of hemoglobin, 42 mg. of urea, 236 mg. of cholesterol, 614 mg. of chloride (expressed as sodium chloride) and 4.6 Gm. of serum protein. The carbon dioxide-combining power was 63.6 volumes per cent. The albumin-globulin ratio was 1.1:1. A diagnosis of subacute or chronic glomerulonephritis with edema and mild secondary anemia was made.

Without any therapy other than rest in bed and a salt-free, high protein diet, the urinary volume per twenty-four hours soon increased to as much as 2,000 cc. and the daily excretion of sodium chloride amounted to approximately 4 Gm. By the morning of the fifth day (fig. 5) the patient had lost 5.1 Kg. (11.2 pounds) of weight and more than 12 Gm. of sodium chloride. When subsequently potassium nitrate was administered, his improvement continued at an even more rapid rate. The maximal urinary volume was 2,500 cc. per twenty-four hours and the

maximal excretion of chloride was 11.2 Gm. in a similar period. When he was dismissed on the nineteenth day, he was free of edema and had lost 15.3 Kg. (approximately 33.7 pounds) of weight and more than 126 Gm. of sodium chloride. Shortly before dismissal of the patient the blood per hundred cubic centimeters contained 578 mg. of chloride (expressed as sodium chloride) and 6 Gm. of serum proteins. The carbon dioxide-combining power was 60.7 volumes per cent. The albumin-globulin ratio was 1.2:1.

This case differs from the 4 cases previously described in that the patient's condition was considerably less severe. The concentration of serum proteins was higher than in any of the other cases, and the excretion of sodium chloride and of water, with dietary treatment alone, was considerably more than the intake. In view of the ease with which the

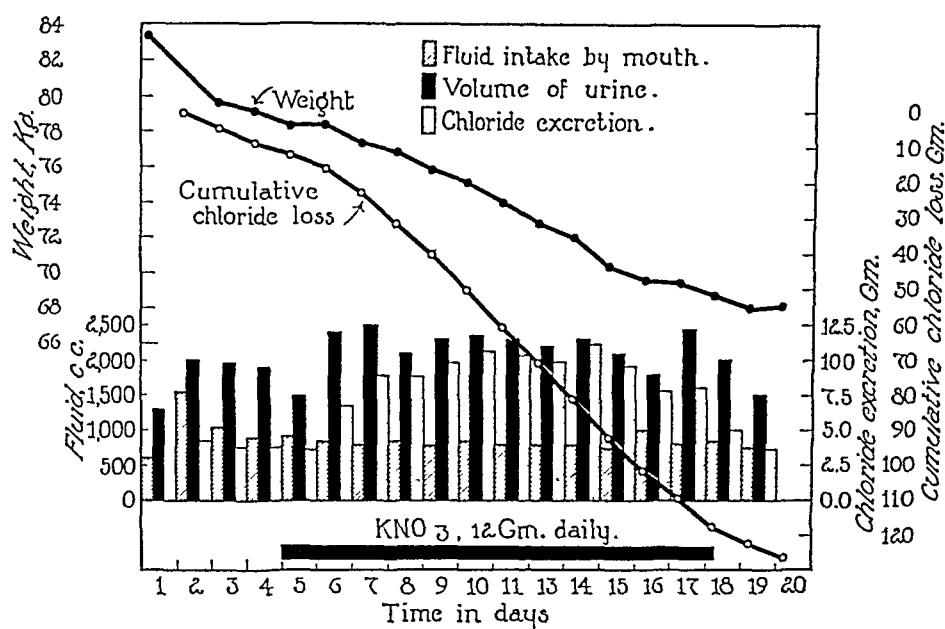


Fig. 5.—Excretion of water and of chlorides by a patient (case 5) who had edema, treated with potassium nitrate administered orally. Daily diet: protein, 80 Gm.; calories, 2,000; salt, none; fluids by mouth, 800 cc.

edema was mobilized, the use of acacia was deemed unnecessary. The response to potassium nitrate was rather typical.

COMMENT

We have previously stated that in the cases of the nephrotic syndrome the major deficiency of renal excretion is in the elimination of sodium chloride and of water. This inability on the part of the kidney appears definitely related to low concentration of serum proteins or to lowered colloid osmotic pressure of the serum. After injection of acacia, judging by the results obtained in the cases presented, the excretion of water and of sodium chloride appears to improve so that considerably more water

and chloride are excreted. Sometimes the concentration of sodium chloride in the twenty-four hour specimen of urine appears to be definitely increased after injection of acacia, and sometimes it does not. Potassium salts in general, the potassium nitrate in particular,⁷ cause an increase in the rate of excretion of sodium and of chloride, and of water as well. The combined use of acacia and potassium nitrate seems to allow removal of edema fluid in a large percentage of adult patients who have the nephrotic type of edema.

The mechanism by which acacia increases the excretion of water and of sodium chloride is unexplained at present. As is well known, intravenous injection of acacia causes an increase in the volume of the circulating blood, and, according to Peters'⁸ suggestion, "It may well be the fullness of the blood stream which provokes the diuretic response on the part of the kidney." Measurements of the actual increase in the volume of the circulating blood after single injections of acacia, such as were performed by Lepore,⁹ show that this increase is of the same order of magnitude as that observed after ingestion of large amounts of water or after intravenous injection of an appreciable volume of a hypertonic solution. Nevertheless, the effects of the latter agents on a patient who has a severe type of nephrotic edema are far from identical with the effects of acacia. In addition, in another condition in which the volume of circulating blood is increased, namely, congestive heart failure, edema is regularly present. Thus, although the increase in the volume of the circulating blood might play an important part in the mobilization of the edema fluid, the mechanism by which this could happen can be described only in general terms. Experimental evidence and quantitative data to substantiate such a descriptive picture are lacking. On the other hand, results of studies on healthy dogs, mentioned earlier, indicated that the excretion of chloride is increased considerably after the administration of acacia.

Renal excretion as interpreted at the present time is effected through glomerular filtration and tubular reabsorption and secretion. In the normal human adult, chloride is supposed to be present in the glomerular filtrate in a concentration essentially similar to its concentration in the plasma. A quantity of approximately 150 cc. is ultrafiltered each minute, and approximately 130 Gm. of sodium chloride passes through the glomerular filter in twenty-four hours. Most of this chloride, of course,

7. Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, *J.A.M.A.* **105**:1584-1591 (Nov. 16) 1935.

8. Peters, J. P.: *Body Water: The Exchange of Fluids in Man*. Springfield, Ill., Charles C. Thomas, Publisher, 1935.

9. Lepore, M. J.: Acacia Therapy in Nephrotic Edema, *Ann. Int. Med.* **11**: 285-296 (Aug.) 1937.

is reabsorbed by the tubules. In patients with the nephrotic syndrome, no essential disturbance of glomerular function, except increased permeability for protein, is supposed to exist. Thus, the difference between the excretion of chloride by the normal person and the excretion by the patient with nephrotic edema must be the result of increased tubular reabsorption of chloride. It is not clear how this excessive reabsorption from the lumen of the tubule into the blood stream could be explained directly by the decreased colloid osmotic pressure of the serum. Nevertheless, little doubt exists that there is a definite cause and effect relation between decreased colloid osmotic pressure and increased tubular reabsorption, because the tendency toward edema and the retention of water and of salt appears to be common to all conditions of advanced hypoproteinemia. Since injections of acacia do not significantly change the colloid osmotic pressure of the serum of patients who have the nephrotic syndrome and since the injection of this substance, judging by experiments on dogs, does not affect the rate of glomerular filtration, it seems to us that the most plausible explanation for the diuretic action of acacia relates to the reestablishment of a more normal rate of tubular reabsorption of water and of chloride.

SUMMARY

Intravenous injection of acacia into 4 patients who had the nephrotic type of edema was followed by marked increases in urinary excretion of water and of chloride (expressed in terms of the sodium salt). This increased excretion of sodium chloride and of water brings about a reversal of conditions which is significant and beneficial, considering the excretion by untreated patients. Neither increases in the volume of the circulating blood nor changes of colloid osmotic pressure appear to account for this change in renal function. Experiments on animals have also demonstrated this increased excretion of chloride after intravenous administration of acacia. It is suggested that an analogous effect might well be responsible for the diuretic response of these patients.

DIAGNOSIS OF CARCINOMA OF THE PANCREAS

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With progressive advance in surgical technic radical but curative operations have been made possible in cases of carcinoma of the pancreas. For these operations to be successfully employed, however, it is of utmost importance that an early diagnosis be made. Yet accuracy of diagnosis at any stage is not great, especially when there is no jaundice or when the body or tail of the pancreas is predominantly involved (table 1). In many cases the disease is incorrectly diagnosed

TABLE 1.—*Diagnostic Accuracy in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Condition Was Correctly D.agnosed Percentage	
1920	Speed, K.: Am. J. M. Sc. 160:1, 1920..	52	3	5.7
1922	Eusterman %	26	8	30.7
		(without jaundice)		
		22	22	100.0
1935	Ransom %	(with jaundice)		
		16	3	18.7
1939	Duff %	(body and tail)		
		16	0	0.0
		(body and tail)		
		132	36	Average 27.2

and its presence is missed in the early stages because in the mind of the average physician certain impressions of traditional diagnostic criteria have persisted despite the fact that they have been repeatedly shown to be false.

This study was undertaken to establish, first, the current leading impressions of the diagnostic criteria of the disease carcinoma of the pancreas, and second, to determine from a review of a series of proved cases observed by my associates and me at the Graduate Hospital of the University of Pennsylvania, as well as of similar series reported in the literature, what the outstanding manifestations of carcinoma of the pancreas really are.

Read before the College of Physicians of Philadelphia, Oct. 28, 1940.

From the Gastrointestinal Service of Dr. Henry L. Bockus, Department of Medicine, Graduate Hospital of the University of Pennsylvania.

To achieve the first aim, a poll was taken among representative groups of fourth year medical students, interns and residents, graduate students and general practitioners in practice five years or less. The poll included 120 persons from thirty-four medical schools, of which three were leading foreign schools. Each person was given an explanation of the nature of the poll being taken but was not told the disease in question. He was then asked to state that feature which he most closely associated with and felt was most commonly to be found and expected in patients with carcinoma of the pancreas.

Many objections may be raised to such a poll. The replies may be said to indicate merely psychologic associations; yet the fact that one given feature is held to be outstanding and characteristic does not mean that other features are not likewise appreciated. This objection and others that might be made are valid beyond question. It should be understood, however, that the poll was meant to determine only common leading impressions and from these to secure a rough index of the trend of diagnostic thought that is uppermost in the minds of younger physicians. Fixed leading impressions of diagnostic criteria must of necessity influence the path of inquiry which any given person will take. In fact, a number of the physicians questioned stated in the course of conversation after the poll that in the absence of the leading and characteristic feature which they associated with carcinoma of the pancreas they would probably fail to think of the disease at all.

It may be seen from this poll (table 2) that 43 per cent of these younger, and presumably better trained, persons expressed the belief that painless jaundice is the most common and characteristic feature of carcinoma of the pancreas. Another 50 per cent stated that simple jaundice is the predominant characteristic, although many qualified the jaundice as being deep and progressive. Only 2.5 per cent expressed the belief that pain is of outstanding consequence. The vast majority (92.5 per cent), therefore, were convinced that jaundice, usually painless and progressive, is the single feature which is paramount in carcinoma of the pancreas.

The second part of this study is based partly on an analysis of the cases of primary carcinoma of the pancreas seen at the Graduate Hospital of the University of Pennsylvania from March 1927 to April 1940. During this period the diagnosis of primary carcinoma of the pancreas was made in 42 cases, in 35 of which it was proved by laparotomy or necropsy. Since 1 of the 35 proved cases has been previously reported,¹ the analysis was restricted to the remaining 34 cases. In 25 of these the diagnosis was confirmed by laparotomy only with positive

1. Yaskin, J. C.: Nervous Symptoms as Earliest Manifestations of Carcinoma of the Pancreas, *J. A. M. A.* **96**:1664 (May 16) 1931.

TABLE 2.—*Poll of Impressions of Chief Diagnostic Criterion in Cases of Carcinoma of the Pancreas*

Status	Number Polled	Number of Different Schools Represented	Diagnostic Criteria																
			Painless Jaundice		Jaundice		Pain		Loss in Weight		Anorexia		Dyspepsia		Enlarged Gallbladder		Deformed Duodenum		Diabetes
Fourth year medical students.	34	4	10	23	1
Interns and residents	36	14	24	10	1	1
Graduate students	26	23	9	14	1	1
General practitioners (In prac- tice 5 years or less)	24	6	9	12	1	..	1	1	..
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Total.....	120	34	52	43.3	59	49.1	3	2.5	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8	0.8
			92.5%				2.5%				5.0%								

findings in biopsy sections in 6, both by laparotomy and by necropsy in 5 and by necropsy alone in 4. To this analysis have been added the findings reported by other authors in similar previous studies.

GENERAL FEATURES

Incidence.—Primary carcinoma of the pancreas is by no means a rare disease. Estimates as to the frequency of its occurrence have been variously made.² On the basis of these it may be stated that primary carcinoma of the pancreas causes 1 to 2 per cent of all deaths in the population at large, is present in about 0.1 per cent of all patients admitted to large general hospitals, is observed at 0.3 to 0.75 per cent of all autopsies and comprises 1 to 2 per cent of all carcinomas.

Sites and Extent of Anatomic Involvement.—Ever since the classic descriptions by Bard and Pic³ and by Chauffard⁴ it has been customary to consider the symptoms of carcinoma of the pancreas as divided into those of carcinoma of the head and those of carcinoma of the body and tail. It is felt that involvement of each area produces manifestations so characteristic as to form a separate syndrome. By the same token, it is believed that the carcinomatous process will affect predominantly one or the other part of the gland.

In a collected series of 1,449 cases the head of the pancreas was involved in 81.7 per cent (table 3). The frequency of involvement of

2. (a) D'Aunoy, R.; Ogden, M. A., and Halpert, B.: Carcinoma of the Pancreas: An Analysis of Forty Autopsies, *Am. J. Path.* **15**:217, 1939. (b) Dublin, L. I.; Kopf, E. W., and Van Buren, G. H.: Cancer Mortality Among Insured Wage Earners and Their Families, New York, Metropolitan Life Insurance Company, 1925, p. 71. (c) Duff, G. L.: The Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas, *Bull. Johns Hopkins Hosp.* **65**:69, 1939. (d) Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 746. (e) Fitcher, T. B.: Cancer of the Pancreas, *Tr. A. Am. Physicians* **34**:284, 1919. (f) Hick, F. K., and Mortimer, H. M.: Carcinoma of the Pancreas, *J. Lab. & Clin. Med.* **19**:1058, 1934. (g) Hoffman, F. L.: Cancer of the Pancreas, *New England J. Med.* **211**:165, 1934. (h) Kiefer, E. D.: Carcinoma of the Pancreas, *Arch. Int. Med.* **40**:1 (July) 1927. (i) Leven, N. L.: Primary Carcinoma of the Pancreas, *Am. J. Cancer* **18**:852, 1933. (j) Marble, A.: Diabetes and Cancer, *New England J. Med.* **211**:339, 1934. (k) McKittrick, L. S., and Root, H. F.: *Diabetic Surgery*, Philadelphia, Lea & Febiger, 1928. (l) Ransom, H. K.: Carcinoma of the Pancreas and Extrahepatic Bile Ducts, *Am. J. Surg.* **40**:264, 1938. (m) Rives, J. D.; Romano, S. A., and Sandifer, F. M., Jr.: Carcinoma of the Pancreas, *Surg., Gynec. & Obst.* **65**:164, 1937. (n) Shapiro, P. F., and Lifvendahl, R. A.: Tumors of the Extra-Hepatic Bile Ducts, *Ann. Surg.* **94**:61, 1931.

3. Bard, L., and Pic, A.: Cancer primitif du pancréas, *Rev. de méd.* **8**:257, 1888.

4. Chauffard, M. A.: Le cancer du corps du pancréas, *Bull. Acad. de méd., Paris* **60**:242, 1908.

the head is less (72.2 per cent) in those cases in which the diagnosis is made from accurate postmortem examinations than in those in which the diagnosis rests solely (93.1 per cent) or to a large extent (79.9 per cent) only on the observations made at the time of operation. Necropsy data indicate that overlapping involvement of various parts of the gland

TABLE 3.—*Incidence of Involvement of Head in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Head Involved	Percentage
Diagnosis at Operation				
1934	Reinhoff and Lewis ^a	87	81	93.1
Diagnosis at Operation or Necropsy				
1922	Eusterman ^{as}	48	33	68.7
1924	Cameron ^{ab}	61	45	73.8
1927	Kiefer ^{2h}	33	28	84.8
1933	Eusterman and Wilbur ^{ah}	70 (without jaundice)	42	60.0
1934	Marble ^{2j}	21	21	100.0
1935	Ransom ⁷	74	58	78.3
1937	Rives, Romano and Sandifer ^{2m}	96	82	85.4
1938	Ransom ²ⁱ	83	65	78.0
1939	MacKinnon ^{9a}	45	42	93.3
1940	Levy and Lichtman ⁵	122	103	84.4
1941	Berk	29	26	89.6
		682	545	Average 79.9
Diagnosis at Necropsy				
1933	Leven ²ⁱ	97	78	80.4
1934	Hick and Mortimer ^{2f}	49	26	51.0
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	31	77.5
1939	Duff ^{2c}	50	31	62.0
1939	Grauer ^{9k}	34	29	85.2
		270	195	Average 72.2
Basis of Diagnosis Not Stated				
1928	Ewing ^{2d}	354	314	88.7
1939	Zollinger and Kevorkian ^{9r}	56	49	87.5
		410	363	88.5
Entire series		1,449	1,184	Average 81.7

is the rule in the vast majority of cases of carcinoma of the pancreas. Even in carefully selected cases diffuse overlapping is apparent. Among 122 verified cases, Levy and Lichtman ⁵ could find but 19 in which

5. Levy, H., and Lichtman, S. S.: Clinical Characterization of Primary Carcinoma of the Body and Tail of the Pancreas, Arch. Int. Med. 65:607 (March) 1940.

they were satisfied that only the body and tail were affected, and yet in some of these there was what they called "terminal" involvement of the head.

It is impossible to estimate accurately the extent of involvement at the operating table. Of 109 patients on whom an operation had been done for carcinoma of the pancreas, Rienhoff and Lewis⁶ were unable to establish the site affected in 22. Of our 34 cases, the site of the carcinomatous process in the pancreas was indeterminate in 5. Yet Ransom,⁷ in presenting 16 cases illustrative of the syndrome to be expected when carcinoma localizes itself to the body and tail, established the localization in 14 cases by means of the operative observations only.

How much even small areas of involvement in a given part of the gland contribute to the symptom picture cannot be evaluated. As will be shown later, even with certain areas dominantly affected the resultant symptom pictures bear much in common, and this may be due to minute but definite overlapping involvement of various parts of the gland.

It is impossible to distinguish at the time of operation between carcinoma of the common duct and carcinoma of the pancreas. Ransom²¹ reported that of 6 patients given an operative diagnosis of carcinoma of the pancreas 3 were proved at necropsy to have carcinoma of the common duct. In 2,500 autopsies Shapiro and Lifvendahl²² encountered carcinoma of the extrahepatic bile ducts three times as frequently as carcinoma of the head of the pancreas, and in 30 autopsies Ransom²¹ found it one and a half times as frequently. Undoubtedly, many disorders considered and recorded as carcinoma of the head of the pancreas are in reality carcinoma of the extrahepatic bile ducts, and the symptom picture presented by them is mistakenly accepted as pathognomonic of involvement of the head of the pancreas.

For these reasons, it was decided to ignore in this analysis any differentiation into carcinoma of the head and of the body and tail. It was deemed better to gather a broad conception of the symptoms and signs to be expected in all cases of carcinoma of the pancreas as they occur consecutively in a general hospital.

Age.—As is true of carcinoma in general, carcinoma of the pancreas is found in the more advanced age groups. The average age in our 34 cases was 59.4 years, whereas the average age in a collected series of 971 cases was 56.4 years (table 4).

6. Rienhoff, W. F., and Lewis, D.: Surgical Affections of the Pancreas Met with in the Johns Hopkins Hospital from 1899 to 1932, Including a Report of a Case of an Adenoma of the Islands of Langerhans, and a Case of Pancreatolithiasis, *Bull. Johns Hopkins Hosp.* **54**:386, 1934.

7. Ransom, H. K.: Carcinoma of the Body and Tail of the Pancreas, *Arch. Surg.* **30**:584 (April) 1935.

Sex.—Carcinoma of the pancreas characteristically affects men more frequently than women. Men comprised 67.6 per cent of the patients in our 34 cases, whereas in a collected series of 1,120 cases men comprised 71.3 per cent, with a ratio of men to women of approximately 2.4:1 (table 5).

Race.—It is commonly accepted that Negroes are relatively immune to carcinoma of the pancreas. A review of various reports studied from

TABLE 4.—*Age Distribution in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Average Age, Yr.	Age Range	Majority Distribution
1858	Da Costa ⁸	37	After 40th year
1919	Futcher ^{2e}	31	34-75	96.7% between 41 and 70
1919	Mussey ^{9s}	90	56.0
1920	Speed, K.: Am. J. M. Sc. 160 :1, 1920..	52	57.0	36-76
1922	Eusterman ^{9g}	48	56.0	32-74
1924	Cameron ^{9b}	61	60.4	30-90
1927	Kiefer ^{2h}	33	56.5	33-76
1928	Friedenwald and Cullen ⁹ⁱ	37	86.4% between 41 and 70
1933	Eusterman and Wilbur ^{9h}	88	72.0% between 40 and 69
1934	Rienhoff and Lewis ⁶	109 (mixed)	25-74	87.1% between 35 and 64
1935	Ransom ⁷	16	57.0	40-69
1937	Rives, Romano and Sandifer ^{2m}	96	58.0	25-84	92.5% between 40 and 79
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	26-80	57.5% over 60
1939	Duff ^{2c}	50	51.2	18-83	32.0% in 6th decade
1939	Grauer ^{9k}	34	91.1% in 5th to 8th decades
1939	MacKinnon ^{9q}	47	56.0	31-80
1939	Zollinger and Kevorkian ^{9y}	49	58.0
1940	Levy and Lichtman ²	19	51.8	24-69
1941	Berk	34	59.4	43-91
		971 (595)*	Average 56.4		

* Number of cases in which average age was noted.

the point of view of racial incidence verified the preponderance of the disease in white persons (table 6). Yet in our cases, despite an admission ratio of white persons to Negroes of 3.5:1, the ratio of incidence of carcinoma of the pancreas was only 2.8:1.

SYMPTOMS

Duration of Symptoms.—Carcinoma of the pancreas is a rapidly advancing disease and hence of relatively short duration. In our group of 34 cases and in a collected series of 849 cases the average duration of

symptoms from their first appearance until the time of hospitalization was six months (table 7). In a similar collected series of 759 cases the average duration of symptoms from onset to death was seven and

TABLE 5.—*Sex Distribution in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Males		Females	
1858	Da Costa ^s	37	22		15	
1919	Futcher ^{2e}	31	22		9	
1919	Mussey ^{9s}	90	72		18	
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920	52	36		16	
1922	Eusterman ^{9g}	48	35		13	
1924	Cameron ^{9h}	61	40		21	
1927	Kiefer ^{2h}	33	18		15	
1928	Friedenwald and Cullen ⁹ⁱ	37	25		12	
1933	Leven ²ⁱ	99	67		32	
1933	Eusterman and Wilbur ^{9h}	88	60		28	
1934	Hick and Mortimer ^{2f}	50	41		9	
1934	Reinhoff and Lewis ⁶	109	81		28	
1935	Ransom ⁷	16	11		5	
1937	Rives, Romano and Sandifer ^{2m}	96	78		18	
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	35		5	
1939	Duff ^{2c}	50	38		12	
1939	Grauer ^{9k}	34	26		8	
1939	MacKinnon ^{9q}	47	23		24	
1939	Zollinger and Kevorkian ^{9y}	49	34		15	
1940	Levy and Lichtman ⁵	19	12		7	
1941	Berk	34	23		11	
Total.....		1,120	No.	%	No.	%
			799	71.3	321	28.7

TABLE 6.—*Racial Incidence in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Whites		Negroes		Admission Ratio Whites
1919	Futcher ^{2e}	31	30		1		7 : 1
1934	Hick and Mortimer ^{2f}	50	45		5		Negroes = 38.4% of all autopsies
1937	Rives, Romano and Sandifer ^{2m}	68	41		27		55 : 45
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	18		22	
1939	Duff ^{2c}	50	36		14	
1941	Berk	34	25		9		3.5 : 1
Total.....		273	No.	%	No.	%	
			195	71.4	78	28.6	

one-tenth months (table 7). This would suggest that most patients have a well advanced stage of the disease by the time they seek hospitalization. It also places doubt on the validity of symptoms dating back as far as three years. In such instances the symptoms of the malignant condition of the pancreas have probably merged imperceptibly into those of some preexistent independent gastrointestinal disturbance.

Initial Symptoms and Signs.—In table 8 are presented the initial symptoms and signs observed in a collected series of 379 cases. It is important to note that the outstanding symptom, which was found in one-half the cases, was abdominal pain. Jaundice, the second most fre-

TABLE 7.—*Duration of Symptoms in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Average Duration (Mo.)	Range
From Onset to Hospitalization				
1922	Eusterman ^{9g}	90	(Few mo.)
	Eusterman ^{9g}	48	4.8
1924	Cameron ^{9b}	61	4.0	11 days to 3 yr.
1927	Kiefer ^{2h}	33	4.3	10 days to 1 yr.
1928	Friedenwald and Cullen ⁹ⁱ	37	8.0	3 mo. to 13 mo.
1933	Eusterman and Wilbur ^{9h}	88	(Less than 6 mo. in 50%)
1934	Marble ^{2j}	21	12.0
1934	Rienhoff and Lewis ⁶	109	...	1 to 12 mo. (87.5%)
1934	Hick and Mortimer ^{2f}	50	6.9	2 wk. to 3 yr.
1935	Keeton ^{9m}	17	(3 to 6)
1935	Ransom ⁷	16	5.7	Longest dur- ation, 1 yr.
1937	Rives, Romano and Sandifer ^{2m}	96	4.8	1 wk. to 2 yr.
1938	Ransom ²ⁱ	83	5.5	2 wk. to 3 yr.
1939	MacKinnon ^{9q}	47	3.6	1 mo. to 9 mo.
1940	Levy and Lichtman ⁶	19	6.7	3 wk. to 3 yr.
1941	Berk	34	6.0	3 wk. to 3 yr.
		849 (545)*	6.0	
From Onset to Death				
1927	Kiefer ^{2h}	31	7.3
1931	Hoffman, F. L.: San Francisco Cancer Survey, Seventh Preliminary Report, Newark, N. J., The Prudential Press, 1931, p. 218	606	10.8
1935	Ransom ⁷	16	10.2
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	4.5	1 mo. to 8 mo.
1939	Duff ^{2c}	16 (body and tail)	5.0
		16 (head)	4.6
1939	Grauer ^{9k}	34	...	1 mo. to 7 yr.
		759 (725)*	7.1	

* Number of cases in which average duration of symptoms was noted.

quent initial symptom, was seen in only one fifth of the cases. In our own group, of the 18 cases in which the order of appearance could be definitely established, pain occurred before jaundice in 15 (83.3 per cent), whereas jaundice appeared before pain in only 3. In 10 of the 18 cases the head was felt to be the dominant site involved, and in 9 of these 10 cases pain was present before jaundice. Kiefer ^{2h} noted that in 16

of 18 cases (88.8 per cent) pain occurred before jaundice. When his cases are combined with ours, it is apparent that in 86.1 per cent of the instances in which both jaundice and pain were present, the pain made its appearance before the jaundice.

TABLE 8.—*Initial Symptoms and Signs in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Symptom or Sign						Gastro-intestinal Disturbances (Flatulency, Etc.)
			Pain	Jaundice	Loss of Weight	Anorexia			
1933	Eusterman and Wilbur ^{9h}	88	30			30
1934	Hick and Mortimer ^{2r}	46	23	6	6	7			..
1937	Rives, Romano and Sandifer ^{2m}	96	58	19
1938	Ransom ²ⁱ	83	39
1939	Duff ^{2c}	16 (body and tail)	14	0	3	4			6
		16 (head)	5	13
1939	Grauer ^{9k}	34	20
		379	No. %	No. %	No. %	No. %	No. %	No. %	No. %
			189 49.8 (379)*	38 21.8 (174)*	9 14.5 (62)*	11 17.7 (62)*	36 34.6 (104)*		

* Number of cases in which the initial symptom or sign was noted.

TABLE 9.—*Chief Complaints in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Pain	Jaundice	Loss in Weight	Anorexia	Weakness	Vomiting	Diarrhea	Constipation
1919	Mussey ^{9s}	90	40	19	Gastric disorders.... ²²					
1927	Kiefer ^{2h}	33	9	17
1935	Keeton ^{9m}	17 (head)	Great majority
1935	Ransom ⁷	16 (body and tail)	13
1940	Berk.....	34	22	12	1	1	2	3	1	2
		190	No. %	No. %	No.				%	
			84 48.5 (173)*	48 30.5 (157)*	32 (124)*				25.8	

* Number of cases in which the complaint was noted.

Chief Complaints.—It is difficult to evaluate chief complaints because of the known effect which pain of any type has on patients. Nevertheless, it is the chief complaints which primarily cause a patient to seek medical attention. It is of great interest, therefore, to note again that abdominal pain was the leading complaint in one half of 190 collected cases (table 9). Jaundice was a chief complaint in less than one

third, and all the other more common complaints combined were presented in only one fourth, of the cases.

Pain.—As early as 1858 Da Costa⁸ stressed the frequency (86.5 per cent) of abdominal pain in a collected series of cases of carcinoma of the pancreas, as well as the characteristics of such pain as it occurs in cases of this disease. Many writers since then have repeatedly emphasized that abdominal pain is often the earliest complaint and during the course of the disease forms the most common and the most prominent symptom.⁹ Despite this, authors of widely used texts either have described pain as usually absent or unimportant¹⁰ or have devoted but passing attention to it,¹¹ and current medical thought still clings to the belief that jaundice, usually of a painless nature, is the outstanding and commonest manifestation of carcinoma of the pancreas (table 2).

Eusterman and Wilbur^{9b} described the following features as typical of the pain in their patients: epigastric situation, radiation to the back,

8. Da Costa, J. M.: Cancer of the Pancreas, *North Am. Med.-Chir. Rev.* **2**:883, 1858.

9. (a) Bourne, G.: Pain as the Only Sign of Pancreatic Carcinoma, *Lancet* **2**:1326, 1936. (b) Cameron, G.: Carcinoma of the Pancreas in Australia, *M. J. Australia* **1**:414, 1924. (c) Donaldson, M.; Cade, S.; Harmer, W. D.; Ward, R. O., and Edwards, A. T.: *The Early Diagnosis of Malignant Disease*, London, Oxford University Press, 1936, p. 106. (d) Duff.^{2c} (e) Dunphy, J. E.: The Early Diagnosis of Cancer of the Pancreas, *Am. J. Digest. Dis.* **7**:69, 1940. (f) Elman, R.: Contributions Made in 1939 to Knowledge in Regard to the Pancreas, *ibid.* **7**:227, 1940. (g) Eusterman, G. B.: Carcinoma of the Pancreas: A Clinical Study of One Hundred and Thirty-Eight Cases, *Tr. Am. Gastro-Enterol. A.* **25**:126, 1922. (h) Eusterman, G. B., and Wilbur, D. L.: Primary Malignant Neoplasm of the Pancreas: A Clinical Study of Eighty-Eight Verified Cases Without Jaundice, *South. M. J.* **26**:875, 1933. (i) Friedenwald, J., and Cullen, T. S.: Carcinoma of the Pancreas: Clinical Observations, *Am. J. M. Sc.* **176**:31, 1928. (j) Futcher.^{2e} (k) Grauer, F. W.: Pancreatic Carcinoma: A Review of Thirty-Four Autopsies, *Arch. Int. Med.* **63**:884 (May) 1939. (l) Hick and Mortimer.^{2f} (m) Keeton, R. W.: Symptoms of Pancreatic Disease and the Mechanism of Their Production, *M. Clin. North America* **18**:1297, 1935. (n) Kiefer.^{2h} (o) Leven.²ⁱ (p) Levy and Lichtman.⁵ (q) MacKinnon, D. C.: Carcinoma of the Pancreas: An Analysis of Forty-Seven Treated Cases from the Lahey Clinic in Boston, *Minnesota Med.* **22**:281, 1939. (r) Mirallié, C.: Cancer primitif du pancréas, *Gaz. d. hôp.* **46**:889, 1893. (s) Mussey, R. D.: Pancreatic Carcinoma, *M. Clin. North America* **3**:681, 1919; (t) Diseases of the Liver, Pancreas and Suprarenal Capsules, in Nothnagel, H.: *Encyclopedia of Practical Medicine*, authorized translation from the German under the supervision of A. Stengel, Philadelphia, W. B. Saunders Company, 1903, vol. 6, pp. 156 and 168. (u) Ranson.^{2j} (v) Ranson.⁷ (w) Rienhoff and Lewis.⁶ (x) Yaskin.¹ (y) Zollinger, R., and Kevorkian, A. Y.: Surgical Aspects of Obstructive Jaundice, *New England J. Med.* **221**:486, 1939.

10. Robson, A. W. M., and Cammidge, P. J.: *The Pancreas: Its Surgery and Pathology*, Philadelphia, W. B. Saunders Company, 1907, p. 514.

11. Opie, E. L.: *Disease of the Pancreas*, Philadelphia, J. P. Lippincott Company, 1910, p. 291.

dull aching character, moderate severity, constancy, steady progression, exaggeration at night and nonrelationship to normal events of the digestive cycle. Kiefer^{2h} described three main types of pain: (1) a steady, dull, severe midepigastric pain radiating to the lower part of the back; (2) a paroxysmal pain beginning near the umbilicus and radiating widely to the back, to the front of the chest and over the abdomen, and (3) a colicky pain usually occurring in the right hypochondrium and sometimes radiating to the right subscapular region. In any patient all of the types might be seen from time to time. Duff,^{2c} on the other hand, expressed the opinion that "there is no constant type or location of pain which is common to all or even to a majority of the cases [of carcinoma of the body or tail of the pancreas], much less any special characteristic of the pain which is peculiar to this disease alone." In our cases all the characters and variations of pain described were exhibited, but we were unable to single out any one common or classic form.

Radiation of the abdominal pain to the back has been remarked on by several observers, who recorded its incidence in percentages ranging from 18 to 50.¹² In some cases lumbar pain is experienced independent of any associated pain in the anterior part of the abdomen. For example, in 1 of our cases the patient was referred to us from the orthopedic department, to which he had been sent because of lumbar pain necessitating the wearing of a brace for three months.

Da Costa⁸ called attention to the relief some patients obtained by stooping or by curving their bodies forward. Chauffard⁴ described some classic positions assumed by patients to obtain relief from pain which he felt were significantly characteristic of a malignant condition of the pancreas. These positions included sitting up, leaning forward in bed, walking with the body leaning or bending forward at the hips and lying curled up on the right side. Lying in bed or assuming the recumbent position frequently intensified the pain,¹³ presumably because this position placed the nervous structures anterior to the vertebral column, especially the solar plexus, under tension. For this reason pain not uncommonly made its first appearance at night and recurred during the night or early morning hours, serving to awaken the patient from sleep. If any feature was outstanding in the pain exhibited in our cases, it was the tendency to appear at night or when a patient was lying down, becoming worse in the back, interfering with sleep and forcing the patient to sit up, bend forward or walk around to secure some relief.

12. Dunphy.^{9e} Eusterman.^{9g} Eusterman and Wilbur.^{9h} Grauer.^{9k} MacKinnon.^{9q} Mirallié.^{9r} Mussey.^{9s} Ransom.⁷ Zollinger and Kevorkian.^{9v}

13. Bourne.^{9a} Cameron.^{9b} Dunphy.^{9e} Eusterman.^{9g} Hick and Mortimer.^{2f} Levy and Lichtman.⁵ Mirallié.^{9r}

The severity of the pain appears to vary, according to the previous reports in the literature. Although most authors agreed that the pain is usually of moderate severity, others described pain of a mild type^{9h} or epigastric distress or uneasiness, in contradistinction to real pain.¹⁴ Ransom²¹ expressed the opinion that the most striking characteristic of the pain was its unusual severity, and Hick and Mortimer^{2f} described it as severe. In evaluating pain in our cases we discarded such complaints as epigastric discomfort and vague colicky or crampy distress and accepted only pain of such severity as to require specific therapy directed toward its relief alone. We, too, were impressed by the degree of severity of the pain manifested. In a number of cases repeated injections of morphine or related analgesics were required to obtain effectual relief.

A classic ulcer rhythm of pain with partial to complete relief with taking of food which was displayed in 4 of our 34 cases (11.7 per cent) led in these cases to a mistaken early diagnosis of peptic ulcer. Eusterman and Wilbur^{9h} described dyspepsia characteristic of ulcer in 12 of 88 cases and Grauer^{9k} obtained a typical history of ulcer in 4 of 34 cases. Carcinomatous invasion of the adjacent portions of the stomach and the duodenum and subsequent ulceration are by no means rare in a primary malignant condition of the pancreas¹⁵ and could easily account for symptoms of ulcer. Likewise, in view of the high incidence of peptic ulcer in any cross section of the population, a benign ulceration might be expected as an independent lesion in some cases of carcinoma of the pancreas. In a few cases, however, in which no demonstrable malignant invasion of the stomach or the duodenum or no other lesion was found at necropsy a definite ulcer syndrome was seen during life.^{9k} This is a misleading feature, which merits a warning remark.

Pain was present at the time of admission to the hospital in 22 of our 34 cases (64.7 per cent) and appeared at some time during the course of observation in 28, or 82.3 per cent (table 10); such an incidence places this symptom second only to loss of weight in frequency of occurrence. In a collected series of 1,181 cases, pain was present at some time or other in 76.4 per cent (table 10). It can be seen from table 10 that pain was more frequent in cases of carcinoma involving only the body and tail than it was in cases of carcinoma involving only the head. Of our 17 cases in which the head of the pancreas was thought to be the only site involved, pain was present at some time during the course of observation in 13 (76.4 per cent), a frequency practically equal to that of jaundice (14, or 82.3 per cent).

14. Da Costa.⁸ Kiefer.^{2h}

15. Da Costa.⁸ Grauer.^{9k} Hick and Mortimer.^{2f} Yaskin.¹

Jaundice.—Attention was previously called to the fact that in approximately 86 per cent of cases pain appeared before jaundice when both symptoms were present and the times of appearance could be deter-

TABLE 10.—*Incidence of Pain at Some Time or Other in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Pain Occurred at Some Time or Other	Percentage
Cases of Involvement of Head Only				
1939	Duff ^{2c}	16	12	75.0
1939	Zollinger and Kevorkian ^{9r}	49	38	77.0
		65	50	Average 76.9
Cases of Involvement of Body or Tail Only				
1935	Ransom ⁷	16	16	100.0
1939	Duff ^{2c}	16	15	93.7
1940	Levy and Lichtman ⁵	19	18	94.6
		51	49	Average 96.1
Admixed Cases				
1858	Da Costa ⁸	37	32	86.5
1893	Mirallié ^{9r}	113	56	49.5
1919	Mussey ^{9s}	90	80	88.8
1919	Futcher ^{2e}	31	25	80.6
1920	Speed, K.: Am. J. M. Sc. 160:1, 1920.....	52	32	61.0
1924	Cameron ^{9b}	61	43	70.5
1927	Kiefer ^{2h}	33	21	63.6
1928	Friedenwald and Cullen ⁹ⁱ	37	31	83.9
1931	Yaskin ¹	4	4	100.0
1933	Leven ²ⁱ	32	32	100.0
1933	Eusterman and Wilbur ^{9h}	88	66	75.0
1934	Rienhoff and Lewis ⁶	109	95	87.2
1934	Marble ^{2j}	21	16	76.1
1934	Hick and Mortimer ^{2f}	46	43	93.4
1935	Keeton ^{9m}	17	14	82.3
1936	Bourne ^{9a}	3	3	100.0
1937	Rives, Romano and Sandifer ^{2m}	93	72	77.4
1938	Ransom ²ⁱ	83	55	66.6
1939	Grauer ^{9k}	34	20	58.8
1939	MacKinnon ^{9q}	47	36	76.5
1941	Berk	34	28	82.3
		1,065	804	Average 75.4
	Entire series	1,181	903	Average 76.4

mined. Other observers have noted that jaundice was not an early sign but appeared at various intervals after the onset of symptoms.¹⁶

16. Ferguson, A. H.: Carcinoma of the Pancreas, Surg., Gynec. & Obst. **10**: 393, 1910. Da Costa.⁸ Dunphy.^{9e} Grauer.^{9k} Keeton.^{9m} Shapiro and Lifvendahl.²ⁿ

At the time of admission to the hospital, jaundice was present in 20 of our 34 cases (58.8 per cent), and in 24 (70.5 per cent) it developed at some time during the course of observation (table 11). This is a

TABLE 11.—*Incidence of Jaundice at Some Time or Other in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Jaundice Present at Some Time or Other	Percentage
Cases of Involvement of Head Only				
1934	Hick and Mortimer ^{2f}	22	19	86.3
1939	Zollinger and Kevorkian ^{9y}	49	42	86.0
1939	Duff ^{2c}	16	13	81.2
1939	D'Aunoy, Ogden and Halpert ^{2a}	31	22	70.9
		118	96	Average 81.3
Cases of Involvement of Body or Tail Only				
1939	Duff ^{2c}	16	8	50.0
1939	D'Aunoy, Ogden and Halpert ^{2a}	9	2	22.2
1940	Levy and Lichtman ⁵	12	4	33.3
		37	14	Average 37.8
Admixed Cases				
1858	Da Costa ⁸	37	22	59.4
1919	Mussey ^{9s}	90	37	41.1
1919	Futcher ^{2e}	29	23	79.3
1920	Speed, K.: Am. J. M. Sc. 160 :1, 1920.....	52	42	80.0
1922	Eusterman ^{9g}	48	22	46.0
1924	Cameron ^{9b}	61	33	54.1
1927	Kiefer ^{2h}	33	25	75.7
1928	Friedenwald and Cullen ⁹ⁱ	37	29	78.4
1933	Eusterman and Wilbur ^{9h}	403	315	78.1
1933	Leven ²ⁱ	32	21	66.6
1934	Rienhoff and Lewis ⁶	109	76	69.7
1934	Hick and Mortimer ^{2f}	46	23	50.0
1934	Marble ^{2j}	21	15	71.4
1937	Rivés, Romano and Sandifer ^{2m}	93	72	77.4
1939	Grauer ^{9k}	34	20	58.8
1939	MacKinnon ^{9q}	47	28	59.5
1941	Berk	34	24	70.5
		1,206	827	Average 68.5
	Entire series	1,361	937	Average 68.8

definitely lesser incidence than that of pain (64.7 per cent on admission and 82.3 per cent during observation). In a collected series of 1,361 cases jaundice was noted in 68.8 per cent, a definitely lesser incidence than that of pain (76.4 per cent).

As might be expected, jaundice was seen less often in those cases of carcinoma involving only the body and tail of the pancreas (37.8 per cent) than it was in those cases of carcinoma involving only the head (81.3 per cent). It is interesting, however, that in approximately one fifth of all cases of the latter type jaundice was not displayed at any time, and it is even more striking that in 48.8 per cent of the cases in which jaundice never developed the carcinoma was in the head of the pancreas (table 11). This figure compares well with that of Eusterman,⁹⁸ who observed that in 42 per cent of 26 cases in which there was

TABLE 12.—*Incidence of Painless Jaundice at Onset or on Admission in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Painless Jaundice Was Present at Onset of Illness or Admission to Hospital	Percentage
1939	Grauer ^{9k}	34	3	8.8
1941	Berk.....	34	9	26.5
		68	12	Average 17.6

TABLE 13.—*Incidence of Painless Jaundice Throughout Course of Observation in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Painless Jaundice Was Present Throughout Course of Observation	Percentage
1919	Mussey ^{9s}	90	6	6.6
1937	Rives, Romano and Sandifer ^{2m}	93	18	19.3
1941	Berk.....	34	6	17.6
		217	30	Average 13.8

no jaundice the head of the pancreas was involved. As* was noted before, of our 17 cases in which the head was felt to be the only site involved jaundice was displayed in 14, or 82.3 per cent, at some time during the course of observation, which incidence is but slightly greater than that of pain (13, or 76.4 per cent).

Painless Jaundice.—Completely contrary to the popular conception of painless jaundice as the classic symptom of carcinoma of the pancreas are the figures shown in tables 12 and 13. It was previously indicated that pain was far and away the commonest initial symptom and was the dominant feature during the course of pancreatic carcinoma. It is not surprising, then, to find, as have several other

investigators,¹⁷ that jaundice without any associated pain is a phenomenon which is not encountered with any great frequency.

Since all forms of mild discomfort were ignored, painless jaundice was felt to be present at the time of admission in 26.5 per cent of our 34 cases but was seen in only 17.6 per cent of a combined series of 68 cases (table 12). Since the incidence of pain increased during the course of observation, the incidence of persistent painless jaundice decreased during the observation period to 17.6 per cent in our cases and to 13.8 per cent in a collected series of 217 cases (table 13).

TABLE 14.—Incidence of Loss in Weight in Cases of Carcinoma of the Pancreas

Year	Author	Number of Cases	Number in Which Loss in Weight Occurred	Percentage	Average Loss in Weight (Lb.)	Average Rate of Loss in Weight (Lb. per Week)
1919	Futcher ^{2c}	31	29	93.5
1920	Speed, K.: Am. J. M. Sc. 160 :1, 1920....	52	47	90.0
1922	Eusterman ^{2g}	90	26	..
	Eusterman ^{2g}	48	29	..
1924	Cameron ^{2b}	61	43	70.5
1927	Kiefer ^{2h}	33	28	84.8	28	5
1933	Leven ²¹	32	32	100.0	..	10
1934	Rienhoff and Lewis ⁶	109	94	86.2
1934	Hick and Mortimer ^{2f}	46	43	93.4
1934	Marble ^{2j}	21	18	85.7
1935	Ransom ⁷	16	16	100.0	..	5.25
1937	Rives, Romano and Sandifer ^{2m}	56	50	89.2
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	Practically all
1939	Duff ^{2c}	16 (body and tail)	16	100.0
		16 (head)	Majority
1939	MacKinnon ^{2q}	47	40	85.1	22.7	..
1939	Zollinger and Kevorkian ^{2r}	49	41	86.0	(7 per mo.)
1940	Levy and Lichtman ⁵	19	16	84.2
1941	Berk.....	31	28	90.1
		813 (619)*	541	Average 87.4	26.4	6.8

* Total number of cases in which loss of weight was noted.

Loss of Weight.—Loss of weight is the most frequent symptom found in cases of carcinoma of the pancreas. It was present in 90.1 per cent of our cases at the time of admission and was noted at some time during the illness in 87.4 per cent of a collected series of 813 cases (table 14). The loss of weight in cases of this disease is characteristically rapid and great. In the same series of collected cases the total loss averaged 26.4 pounds (11.9 Kg.), with an average loss of 6.8 pounds (3.1 Kg.) per week (table 14).

17. Dunphy.^{2e} Grauer.^{2k} Leven.²¹ Mussey.^{2s} Ransom.²¹ Shapiro and Lifvendahl.²ⁿ

Fatigue and Weakness.—Associated with the prominent loss of weight and with cachexia are fatigue and weakness. These were noted at the time of admission in 78.3 per cent of our cases and at some time in 51.1 per cent of a collected series of 186 cases (table 15).

Anorexia.—Loss of appetite was a complaint at the time of admission in 40.9 per cent of our cases and at some time in 44.4 per cent of a collected series of 290 cases (table 16).

TABLE 15.—*Incidence of Fatigue and Weakness in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Fatigue and Weakness Was Present	Percentage
1927	Kiefer ^{2b}	33	21	63.6
1934	Marble ^{2j}	21	9	42.8
1934	Rienhoff and Lewis ^a	109	47	43.1
1941	Berk.....	23	18	78.3
		186	95	Average 51.1

TABLE 16.—*Incidence of Anorexia in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Anorexia Was Present	Percentage
1858	Da Costa ⁸	25	7	28.0
1924	Cameron ^{9b}	61	17	27.9
1927	Kiefer ^{2b}	33	20	60.6
1934	Marble ^{2j}	21	6	28.5
1934	Hick and Mortimer ^{2f}	46	30	65.0
1935	Ransom ⁷	16	3	18.7
1939	MacKinnon ^{9a}	47	19	40.2
1940	Levy and Lichtman ⁵	19	18	94.7
1941	Berk.....	22	9	40.9
		290	129	Average 44.4

Nausea and Vomiting.—Nausea alone, vomiting alone or nausea and vomiting together occurred in 42.3 per cent of a collected series of 759 cases (table 17). In several of our own cases and in a number of the cases reported by others, persistent vomiting could be attributed to obstruction of the pylorus or the duodenum by the malignant growth in the pancreas. Because of the ease with which these areas lend themselves to encroachment and compression by pancreatic tumors, it is not surprising that in some patients intestinal obstruction is one of the earliest manifestations of a primary pancreatic neoplasm.

Constipation.—Constipation is a fairly common and often an early complaint in cases of carcinoma of the pancreas. In 43.3 per cent of our cases the patients were constipated for the first time in their lives when they were admitted to the hospital or were much more severely constipated than they had ever been previously. Constipation of like character was present at some time in 38.7 per cent of a collected series of 573 cases (table 18).

TABLE 17.—*Incidence of Nausea and Vomiting in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Symptom Was Present	Percentage
Nausea Alone				
1927	Kiefer ^{2h}	33	20	60.6
1934	Hick and Mortimer ^{2f}	46	10	21.7
1939	MacKinnon ^{9a}	47	10	21.2
1941	Berk.....	23	11	47.8
		149	51	Average 34.2
Vomiting Alone				
1858	Da Costa ⁸	37	21	56.7
1919	Futcher ^{2e}	31	10	32.2
1924	Cameron ^{9b}	61	23	37.7
1934	Hick and Mortimer ^{2f}	46	16	34.8
1939	MacKinnon ^{9a}	47	13	17.0
1939	Zollinger and Kevorkian ^{9y}	49	18	37.0
1940	Levy and Lichtman ⁶	19	2	10.5
1941	Berk.....	31	13	41.9
		321	116	Average 36.1
Nausea and Vomiting				
1933	Leven ²ⁱ	32	18	56.0
1934	Rienhoff and Lewis ⁶	109	72	66.1
1934	Marble ^{2j}	21	9	42.8
1937	Rives, Romano and Sandifer ^{2m}	93	44	47.3
1939	Grauer ^{9k}	34	11	32.3
		289	154	Average 53.2
	Entire series.....	759	321	Average 42.3

Diarrhea.—Diarrhea, usually of an intermittent character, proved to be a not infrequent symptom in cases of carcinoma of the pancreas. At the time of admission diarrhea was or had been present in 30 per cent of our 34 cases, although in a collected series of 679 cases it was present in only 10.8 per cent (table 19). Its frequency as a symptom in cases of carcinoma of the pancreas is, therefore, one third that of constipation. This is in sharp contrast to the ratio of constipation to diarrhea in routine office practice, which is approximately

10:1. Friedenwald and Cullen ⁹¹ called attention to a small group of cases in which definite signs were preceded by persistent diarrhea. The authors expressed the belief that this occurs frequently enough to

TABLE 18.—*Incidence of Constipation in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Constipation Was Present	Percentage
1858	Da Costa ⁸	34	19	55.8
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920.....	52	19	36.5
1924	Cameron ^{9b}	61	25	40.9
1927	Kiefer ^{2h}	33	16	48.4
1934	Hick and Mortimer ^{2f}	46	17	36.9
1934	Rienhoff and Lewis ⁹	109	30	27.5
1935	Ransom ⁷	16	13	81.2
1937	Rives, Romano and Sandifer ^{2m}	93	31	33.0
1938	Ransom ²¹	83	(28+)	33.3+
1939	Duff ^{2c}	16	11	68.7
1941	Berk.....	30	13	43.3
		573	222	Average 38.7

TABLE 19.—*Incidence of Diarrhea in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Diarrhea Was Present	Percentage
1858	Da Costa ⁸	34	3	8.8
1919	Futcher ^{2e}	31	1	3.2
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920.....	52	3	5.7
1924	Cameron ^{9b}	61	8	13.1
1927	Kiefer ^{2h}	33	0	0.0
1928	Friedenwald and Cullen ⁹¹	37	6	16.2
1934	Marble ^{2j}	21	4	19.0
1934	Hick and Mortimer ^{2f}	46	1	2.1
1934	Rienhoff and Lewis ⁹	109	5	4.6
1935	Keeton ^{9m}	30	5	16.6
1937	Rives, Romano and Sandifer ^{2m}	93	19	20.0
1938	Ransom ²¹	83	10	12.5
1940	Levy and Lichtman ⁵	19	0	0.0 ..
1941	Berk.....	30	9	30.0
		679	74	Average 10.8

warrant the conclusion that whenever persistent diarrhea which cannot be accounted for by the usual causes is observed in a person during middle life carcinoma of the pancreas should be suspected. In 2 of our cases intermittent diarrhea heralded the appearance of other signs and symptoms.

Nervous Phenomena.—Yaskin¹ first called attention to the presence in cases of pancreatic carcinoma of early symptoms which were largely psychic. Latter and Wilbur¹⁸ and Dunphy^{9e} reported similar cases. The essential features described by Yaskin consisted of: anxiety; obstinate insomnia not ascribable to pain or relieved by the usual somnifacients; depression, with crying spells, conviction of imminent physical danger; absence of feelings of unreality, and absence of disturbances in perception, memory, orientation or judgment. The importance of appreciating that such mental phenomena occur rests on the fact that patients who experience them are invariably labeled as psychoneurotic when they complain of abdominal pain or of pain in the back in addition to their psychic symptoms. The true condition goes unsuspected until jaundice makes a belated appearance, at which time little can be done therapeutically.

One of Yaskin's cases was reported from this hospital, and, exclusive of that case, psychic phenomena of the type described were seen in 3 of our 34 cases.

PHYSICAL FINDINGS

Palpable Liver.—Bard and Pic³ stressed that the liver of a patient with carcinoma of the head of the pancreas was characteristically not enlarged. The liver was palpable in over three fourths (78.8 per cent) of our cases and in almost two thirds (63.2 per cent) of a collected series of 454 cases (table 20). It cannot be said, of course, that all livers which are barely palpable are always enlarged. Rives and his associates^{2m} noted that of 41 cases in which necropsy was done the liver appeared enlarged clinically in 51 per cent, while enlargement was apparent at necropsy in only 21 per cent. Furthermore, concomitant jaundice and hepatic metastasis affect in varying degree the size of the liver and the ease with which it can be felt. Nevertheless, the fact that so many livers can be felt casts doubt on the truth or value of the classic impression that the liver is not enlarged in cases of carcinoma of the head of the pancreas.

Distended Gallbladder.—A time-honored concomitant of the traditional painless jaundice described in cases of carcinoma of the pancreas is distention of the gallbladder in accordance with the law of Courvoisier. A distended gallbladder could be felt clinically in 41.6 per cent of our 24 cases with associated jaundice (table 21), and in one fourth (24.2 per cent) of all 34 cases, including those with and those without associated jaundice, was an enlarged gallbladder found on

18. Latter, K. A., and Wilbur, D. L.: Psychic and Neurologic Manifestations of Carcinoma of the Pancreas, Proc. Staff Meet., Mayo Clin. 12:457, 1937.

physical examination. In a collected series of cases a distended gallbladder could be demonstrated clinically in one half (50.9 per cent) of 175 cases with associated jaundice (table 21) and one third (37.5 per cent) of 729 cases with or without associated jaundice. The number of

TABLE 20.—*Incidence of Palpable Liver in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Liver Was Palpable	Percentage
1919	Futcher ^{2c}	31	12	38.7
1924	Cameron ^{9b}	61	29	47.5
1927	Kiefer ^{2h}	33	26	78.9
1928	Friedenwald and Cullen ⁹ⁱ	37	17	45.9
1933	Leven ²ⁱ	32	26	81.0
1937	Rives, Romano and Sandifer ^{2m}	93	61	65.5
1939	Duff ^{2c}	32	23	71.8
1939	Grauer ^{9k}	34	15	44.1
1939	Zollinger and Kevorkian ^{9r}	49	39	80.0
1940	Levy and Lichtman ⁵	19	13	68.4
1941	Berk.....	33	26	78.8
		454	287	Average 63.2

TABLE 21.—*Incidence of Distended Gallbladder in Cases of Carcinoma of the Pancreas with Jaundice*

Year	Author	Number of Cases	Number in Which Gallbladder Was Palpable Clinically	Percentage	Number in Which Gallbladder Was Found Distended at Laparotomy or Necropsy	Percentage
1919	Mussey ^{9s}	37	31	83.7
1922	Eusterman ^{9g}	22	11	50.0	20	90.0
1927	Kiefer ^{2h}	23	15	65.2
1933	Leven ²ⁱ	20	14	70.0
1939	Duff ^{2c}	21	6	28.5
1939	MacKinnon ^{9q}	28	25	89.2
1941	Berk.....	24	10	41.6
		175 (110, clinically) (67, laparotomy or necropsy)	56 (110, clinically) (67, laparotomy or necropsy)	Average 50.9	76	Average 87.3

gallbladders found distended at the time of operation or autopsy, however, was much greater than the number which could be felt on examination. In the collected series, evidence of distention of the gallbladder was obtained at laparotomy or necropsy in 87.3 per cent of the 175 cases with associated jaundice (table 21) and in 66.6 per cent of the 729 cases with or without associated jaundice. Courvoisier's law, there-

fore, would appear to be of even more value to the surgeon at the time of operation than to the clinician during the physical examination.²¹

Pancreatic Mass.—The retroperitoneal location of the pancreas renders that organ relatively inaccessible to ordinary palpation. In a number of instances we could feel abdominal masses in the general area that the pancreas might be expected to occupy, but, accepting only instances in which other possible sites were fairly well excluded, we could definitely feel a pancreatic mass in only 12.1 per cent of cases (table 22). Of a collected series of 707 cases, a pancreatic mass was said to have been palpated in 37.3 per cent (table 22).

TABLE 22.—*Incidence of a Palpable Pancreatic Mass in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Pancreatic Mass Was Palpable	Percentage
1858	Da Costa ⁸	37	13	35.1
1919	Futcher ^{2e}	31	12	38.7
1919	Mussey ^{9s}	90	50	56.0
1922	Eusterman ^{9g}	48	20	41.6
1924	Cameron ^{9b}	61	23	37.7
1927	Kiefer ^{2h}	33	9	27.2
1928	Friedenwald and Cullen ⁹ⁱ	37	16	43.2
1933	Leven ²ⁱ	32	7	21.8
1933	Eusterman and Wilbur ^{9h}	88	52	59.1
1935	Ransom ⁷	16	8	50.0
1938	Ransom ²ⁱ	83	32	38.5
1939	Duff ^{2c}	16	2	12.5
1939	Grauer ^{9k}	34	2	5.8
1939	Zollinger and Kevorkian ^{9r}	49	5	9.0
1940	Levy and Lichtman ⁵	19	9	47.3
1941	Berk.....	33	4	12.1
		707	264	Average 37.3

A number of investigators have called attention to the fact that pancreatic masses may be movable, despite their deep position.¹⁹ We were able to confirm this in 2 cases.

Ascites.—Ascites may develop in cases of pancreatic carcinoma as a result of metastases into the peritoneum or into the liver, hypoproteinemia, thrombosis of the portal vein or compression of the portal vein by lymph nodes or by malignant tissue. Whether the ascitic fluid is hemorrhagic or clear depends on its cause. As might be expected, ascites was found with greater frequency at operation or at autopsy (35.2 per

19. Eusterman and Wilbur.^{9h} Friedenwald and Cullen.⁹ⁱ Kiefer.^{2h} Levy and Lichtman.⁵

cent) (table 23) than it was clinically (15.6 per cent). It was felt to be present clinically in 4 of our 34 cases (11.7 per cent). When the cases in which ascites was observed clinically and those in which it was found at operation or necropsy were combined, it was found that ascites was reported in 23.7 per cent of 737 cases (table 23).

TABLE 23.—Incidence of Ascites in Cases of Carcinoma of the Pancreas

Year	Author	Number of Cases	Number in Which Ascites Was Present	Percentage
Preoperative or Antemortem Diagnosis				
1893	Mirallié ^{9c}	113	13	11.5
1919	Futcher ^{2e}	31	4	12.9
1920	Speed, K.: Am. J. M. Sc. 160:1, 1920.....	52	10	20.0
1922	Eusterman ^{9g}	22	4	18.1
1924	Cameron ^{9b}	61	10	16.4
1927	Kiefer ^{2h}	33	3	9.0
1933	Leven ²ⁱ	32	7	21.8
1934	Marble ^{2j}	21	6	28.5
1935	Keeton ^{9m}	30	6	20.0
1941	Berk.....	34	4	11.7
		429	67	Average 15.6
Postoperative or Postmortem Diagnosis				
1922	Eusterman ^{9g}	22	10	45.4
1933	Leven ²ⁱ	99	48	48.4
1934	Hick and Mortimer ^{2f}	46	8	17.4
1935	Ransom ⁷	16	3	18.7
1939	Duff ^{2c}	32	11	34.3
1939	Grauer ^{9k}	34	8	23.5
1939	D'Aunoy, Ogden and Halpert ^{2a}	40	14	35.0
		289	102	Average 35.2
Basis of Diagnosis Not Definitely Stated				
1940	Levy and Lichtman ⁵	19	6	31.5
	Entire series.....	737	175	Average 23.7

LABORATORY DATA

Disturbed Carbohydrate Metabolism.—Glycosuria: Glycosuria as a manifestation of disturbed carbohydrate metabolism in cases of carcinoma of the pancreas has been appreciated for a long time. Nevertheless, the frequency with which this has been reported is definitely greater since 1928 than before that time. This is a reflection, perhaps, of an increasing recourse to laboratory tests as instruments of diagnosis. Glycosuria was present prior to operation or necropsy in 24.2 per cent of our cases, whereas in only 9.4 per cent of a collected series of 692 cases was

glycosuria evidenced at some time (table 24). The collected series dates back to 1893, however, and includes the low percentages of the earlier reports.

Hyperglycemia: Hyperglycemia occurred with about the same frequency (27.3 per cent) in our cases as did glycosuria (table 25). In

TABLE 24.—*Incidence of Glycosuria in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Glycosuria Was Present	Percentage
1893	Mirallié ⁹¹	50	13	26.0
1919	Futcher ^{2e}	31	3	9.7
1919	Mussey ^{9s}	90	4	4.4
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920.....	52	3	5.7
1922	Eusterman ^{9g}	48	5	10.4
1924	Cameron ^{9b}	61	2	3.3
1927	Kiefer ²¹	33	2	6.0
1928	Friedenwald and Cullen ⁹¹	37	6	16.0
1933	Leven ²¹	32	3	9.3
1935	Keeton ^{9m}	30	3	10.0
1935	Ransom ⁷	16	2	12.5
1937	Rives, Romano and Sandifer ^{2m}	96	2	2.0
1938	Ransom ²¹	83	9	10.7
1941	Berk.....	33	8	24.2
		692	65	Average 9.4

TABLE 25.—*Incidence of Hyperglycemia in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Hyperglycemia Was Present	Percentage
1933	Leven ²¹	32	5	15.6
1935	Rives, Romano and Sandifer ^{2m}	96	9	9.3
1935	Keeton ^{9m}	30	6	20.0
1938	Ransom ²¹	35	6	17.1
1939	Grauer ^{9k}	14	8	57.1
1940	Levy and Lichtman ⁶	12	6	50.0
1941	Berk.....	33	9	27.3
		252	49	Average 19.4

the collected series, on the other hand, hyperglycemia was twice as frequent (19.4 per cent of 252 cases) as glycosuria. The data on hyperglycemia, it should be pointed out, were drawn from reports made between 1933 and 1940, years during which the reported incidence of glycosuria was also definitely greater.

Impaired Dextrose Tolerance: Impairment of carbohydrate metabolism seems to be best revealed by means of a dextrose tolerance test.

We have encountered instances, just as have others reporting on the subject, in which there was neither glycosuria nor hyperglycemia, yet in which a definitely impaired tolerance to dextrose could be demonstrated. In our hands the test has yielded a surprisingly high percentage (77.8) of positive results in the cases in which it has been employed (table 26), and we have come to rely on the demonstration of impaired dextrose tolerance as of great diagnostic importance in cases of suspected carcinoma of the pancreas. The experience of other investigators has varied, so that in only 20.8 per cent of a collected group of 163 cases was an impaired tolerance to dextrose displayed (table 26). Nevertheless, this figure represents a greater incidence than that recorded for either glycosuria or hyperglycemia alone.

TABLE 26.—*Incidence of Impaired Dextrose Tolerance in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Impaired Dextrose Tolerance Was Present	Percentage
1922	Eusterman ¹⁸	48	5 (approximately)	10.4 (approximately)
1928	Friedenwald and Cullen ¹⁹	4	4	100.0
1934	Hick and Mortimer ²⁰	46	8	17.8
1935	Ransom ⁷	16	1	6.2
1938	Ransom ²¹	35	6	17.1
1939	Grauer ²²	2	1	50.0
1940	Levy and Lichtman ⁶	3	2	66.6
1941	Berk.....	9	7	77.8
		163	34	Average 20.8

In this regard, Marble,²³ after a review of the literature on carbohydrate metabolism in nondiabetic patients with carcinoma, concluded that the bulk of evidence seems to indicate that in a large percentage of cases of carcinoma of any type, certain rather slight, though definite abnormalities in sugar tolerance curves are obtained. Reduced intake of food, metastases to the liver, the hepatic changes incident to prolonged biliary obstruction and potential diabetes are factors which act independently of the carcinoma itself to influence dextrose tolerance. We witnessed in 1 case the return of a normal dextrose tolerance curve after cholecystogastrostomy, and in a number of other cases the degree of impairment of carbohydrate metabolism seemed less after palliative operations than in no way affected the primary neoplasm itself.

Combined Defects in Carbohydrate Metabolism: Of our cases in which suitable determinations were made, both glycosuria and hypo-

glycemia were present in 18.2 per cent (6 of 33), a combination of glycosuria, hyperglycemia and impaired dextrose tolerance in 33.3 per cent (3 of 9), and glycosuria or hyperglycemia or an impaired dextrose tolerance curve in 41.8 per cent (14 of 33). These figures illustrate the diagnostic value of some demonstrable defect in carbohydrate metabolism in cases of suspected pancreatic carcinoma.

Precedent Diabetes Mellitus.—In a number of cases in which some form of defective carbohydrate metabolism was demonstrated diabetes was known to exist. The predisposing role of diabetes mellitus in cases of carcinoma of the pancreas has long attracted speculative attention but is still a mooted problem. A number of investigators have expressed the belief that any association between the two conditions is purely coincidental²⁰ and is probably to be explained by the fact that both

TABLE 27.—*Incidence of Precedent Diabetes Mellitus in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Precedent Diabetes Mellitus Was Present	Percentage
1924	Cameron ^{2b}	61	1	1.6
1933	Leven ²¹	32	2	6.2
1934	Hick and Mortimer ²¹	46	3	6.5
1938	Ransom ²¹	83	6	7.2
1940	Levy and Lichtman ²	19	3	15.7
1941	Berk.....	31	4	11.7
		275	19	Average 6.9

diseases have their maximum incidence in the same age groups. Marble,^{2j} on the contrary, found that of 256 malignant conditions in 10,000 persons proved to have diabetes 33, or 13 per cent, were carcinoma of the pancreas, and McKittrick and Root^{2k} found that 32.4 per cent of 37 malignant conditions in 2,179 persons proved to have diabetes were carcinoma of the pancreas. The pancreas was far and away the most common site of a malignant condition in these diabetic patients, and the aforementioned percentages (13 and 32.4) indicate a distinctly greater incidence than that of pancreatic carcinoma in the population at large (1 to 2 per cent of all carcinomas).

In 11.7 per cent of our cases there was a history of long-standing diabetes mellitus, while in 6.9 per cent of a collected series of 275 cases there was a history of such a condition (table 27).

20. Kiefer,^{2h} Ransom,²¹

Anemia.—Despite the rapid wasting and the cachexia displayed in cases of carcinoma of the pancreas, it is remarkable how slight an anemia is present. This fact is in marked contrast to the usual finding in cases of a malignant condition of the gastrointestinal tract in general and might prove of some value in the differential diagnosis of these two types of lesions. In 75.8 per cent of our cases the red cell count was less than 4,500,000 per cubic millimeter of blood at the time of admission to the hospital (table 28). In only 32.4 per cent of a collected series of 292 cases was anemia displayed, although the several reports varied in the severity of criteria. The average red cell count in our cases was 4,080,000, and in the collected series 4,040,000 per cubic millimeter

TABLE 28.—*Incidence of Anemia in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Anemia Was Present	Percentage	Average Red Cell Count, Millions	Average Hemoglobin Concentration, Percentage
1927	Kiefer ^{2h}	22	9 (less than 4,000,000 red cells)	42.8
1933	Eusterman and Wilbur ^{oh}	88	12 (approximately)	13.0+
1933	Leven ²ⁱ	32	79.4
1935	Ransom ^r	16	75.0
1938	Ransom ²ⁱ	83	4,000,000	74.0
1940	Levy and Lichtman ^r	18	80.7
1941	Berk.....	33	25 (less than 4,500,000 red cells)	75.8	4,080,000	69.5
		292 (142)*	46	Average 32.4	4,040,000	75.7

* Total number of cases in which anemia was noted.

of blood. The concentration of hemoglobin tended to run lower than the red cell counts, which discrepancy resulted in hypochromia. The average hemoglobin concentration was 69.5 per cent in our cases and 75.7 per cent in the collected series (table 28).

Roentgenologic Findings.—The roentgenogram has proved of inestimable value in establishing the diagnosis of pancreatic carcinoma prior to operation. The data in table 29 demonstrate how the accuracy of roentgenologic diagnosis and the percentage of positive findings have increased in recent years.

In our experience the most common signs of a malignant condition of the pancreas were: (1) obstruction at some part of the duodenum, usually the third part, or at the pylorus, with stasis in the proximal parts; (2) irregularity and deformity of the pylorus and the duodenum from infiltrative encroachment, and (3) widening of the sweep of the duodenum.

In 14, or 45.2 per cent, of the 31 of our cases in which roentgenograms of the gastrointestinal tract were made, there were changes which warranted the roentgenologist's suggestion that a malignant condition existed in or about the pancreas (table 29). If we were to include, in addition, those cases in which no mention was made of a malignant condition at the time of the examination but in which, in retrospect, suggestive signs were apparent, the number in which there were positive findings would be increased to 20, or 64.5 per cent. Positive findings were noted in 37 per cent of a collected series of 367 cases (table 29).

TABLE 29.—Incidence of Positive Roentgen Ray Findings in Cases of Carcinoma of the Pancreas

Year	Author	Number of Cases	Number in Which Positive Roentgen Ray Findings Were Present	Percentage
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920.....	23	2	8.7
1927	Kiefer ^{2h}	13	0	0.0
1933	Leven ²ⁱ	24	6	25.0
1933	Eusterman and Wilbur ^{9h}	68	32	47.0
1935	Ransom ⁷	15	4	26.6
1937	Rives, Romano and Sandifer ^{2m}	50	23	46.0
1938	Ransom ²ⁱ	93	24	25.8
1939	Duff ^{2c}	20	10	50.0
1939	MacKinnon ^{9a}	21	15	71.4
1940	Levy and Lichtman ⁵	9	6	66.6
1941	Berk.....	31	14	45.2
		367	136	Average 37.0

Pancreatic Enzymes in Blood.—Johnson and Bockus ²¹ have incorporated into a recent report their experiences in the study of diseases of the pancreas by means of determining serum lipase concentrations. According to their technic, values of serum above 1 cc. of a twentieth-normal solution of sodium hydroxide are indicative of some abnormal condition in the pancreas. Determinations of serum lipase were made by them in 11 of the 34 cases of malignant conditions of the pancreas analyzed in this report. Concentrations in excess of 1 cc. of a twentieth-normal solution of sodium hydroxide were obtained in 6 cases. In 4 cases the abnormal levels were obtained prior to operation and in 2 only after the diagnosis had been established at operation. The preoperative positivity, therefore, was 36.1 per cent, and the positivity

21. Johnson, T. A., and Bockus, H. L.: Diagnostic Significance of Determinations of Serum Lipase, Arch. Int. Med. **66**:62 (July) 1940.

of the test at some time or other in the course of the disease was 54.5 per cent. Comfort and Osterberg,²² using a little higher standard for normal lipasemia (1.5 cc. of a twentieth-normal solution of sodium hydroxide), recently reported 40.5 per cent accuracy for elevations of serum lipase and 8.0 per cent accuracy for elevation of serum amylase in cases of carcinoma of the pancreas. These simple determinations, particularly the concentration of serum lipase, hold forth much promise as diagnostic aids in cases of pancreatic carcinoma. A greater percentage of positivity will probably be obtained as the tests are done more frequently and earlier in cases of suspected carcinoma of the pancreas.

Bloody Stools.—The absence of blood in stools has been advanced as an aid in the differential diagnosis of pancreatic carcinoma and carcinoma of the gastrointestinal tract, with which the former might be confused. As a matter of fact, this criterion is not entirely reliable. Although gross bleeding in cases of carcinoma of the pancreas is uncommon, it has been reported.²³ Requiring that two or more stools yield plus 3 or stronger reactions to the Gregerson test before they were considered positive for occult blood, we were able to find occult blood in the stools in 26.9 per cent of our cases (table 30). Of a collected series of 424 cases blood was found in the stools in 27.5 per cent (table 30).

Fatty Stools.—Large, bulky, fermenting, fatty, greasy or buttery stools are traditionally associated with carcinoma of the pancreas. Actually, however, such stools are rare. Defining a fatty stool as one either macroscopically fatty in appearance or one exhibiting microscopically a plus 4 reaction for neutral fat, fatty acids or soap on two or more occasions, we were able to find fatty stools before operation or necropsy in only 4 per cent of our cases. Although in 9.7 per cent of a collected series of 680 cases (table 31) fatty stools were displayed at some time, the other diagnostic criteria in many instances were such that the mere presence of microscopic amounts of fat was sufficient to warrant the stools being designated as fatty. Coffey, Mann and

22. Comfort, W. W., and Osterberg, A. E.: The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, Proc. Staff Meet., Mayo Clin. **15**:427, 1940.

23. Adler, F. H.: Carcinoma of the Pancreas with Ulceration into the Gastro-Intestinal Tract, J. A. M. A. **76**:158 (Jan. 15) 1921. Duff,^{2c} Eusterman.^{9g} Ochsner, H. C., and Wilbur, D. L.: Malignant Lesions Involving the Duodenum as a Causative Factor in Gastro-Intestinal Hemorrhage, Proc. Staff Meet., Mayo Clin. **9**:776, 1934. Secousse: Un cas de cancer du pancréas chez un sujet jeune avec terminaison par hémorrhagie intestinale, J. de méd. de Bordeaux **44**:507, 1914. Troisième, J.; Bariéty, M., and Gabriel, P.: Hématémèse par bourgeonnement intraportal d'un cancer pancréatique, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:368, 1934. Yaskin.¹

Bollman ²⁴ were able to demonstrate in dogs that gross alterations of the digestive functions appear only in the complete absence of the external pancreatic secretion and small amounts of pancreas are adequate

TABLE 30.—*Incidence of Blood in Stools in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Blood Was Present in Stools	Percentage
1858	Da Costa ^s	34	3	8.8
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920.....	52	16	30.0
1927	Kiefer ^{2h}	27	10	37.0
1933	Leven ²ⁱ	16	6	37.5
1934	Rienhoff and Lewis ⁶	109	23	21.1
1935	Ransom ⁷	8	4	50.0
1938	Ransom ²ⁱ	109	34	31.1
		(only 83 with primary carcinoma of pancreas)		
1939	Duff ^{2c}	32	12	37.5
1940	Levy and Lichtman ⁵	11	2	18.1
1941	Berk.....	26	7	26.9
		424	117	Average 27.5

TABLE 31.—*Incidence of Fatty Stools in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Fatty Stools Were Present	Percentage
1858	Da Costa ^s	34	3	8.8
1893	Mirallié ^{9r}	113	9	7.9
1919	Futcher ^{2e}	31	17	54.8
1920	Speed, K.: Am. J. M. Sc. 160 : 1, 1920.....	52	8	15.0
1924	Cameron ^{9b}	61	1	1.6
1927	Kiefer ^{2h}	33	7	21.2
1928	Friedenwald and Cullen ⁹ⁱ	37	8	21.6
1933	Leven ²ⁱ	32	9	28.1
1934	Marble ^{2j}	21	3	14.2
1934	Hick and Mortimer ^{2f}	46	0	0.0
1935	Ransom ⁷	16	0	0.0
1937	Rives, Romano and Sandifer ^{2m}	96	0	0.0
1938	Ransom ²ⁱ	83	0	0.0
1941	Berk.....	25	1	4.0
		650	66	Average 9.7

to maintain complete digestion. Complete failure of fat digestion, with resultant fatty stools of the greasy type, would be expected, therefore,

24. Coffey, R. J.; Mann, F. C. and Bollman, J. L.: The Influence of the Pancreas on the Utilization of Foodstuffs, Am. J. Digest. Dis. **7**:144, 1940.

only in a few cases of severe and advanced disease in which there was complete destruction of functioning pancreatic tissue.

CONCLUSIONS

Diagnostic accuracy in cases of carcinoma of the pancreas is only about 25 to 30 per cent, despite the need for early and accurate diagnosis.

A good part of this lack of diagnostic efficiency is attributable to persistent false impressions as to the usual picture presented by carcinoma of the pancreas.

Overlapping of the areas anatomically involved is so great in carcinoma of the pancreas that it is better to consider the symptoms presented irrespective of the dominant site affected rather than to divide them into those of carcinoma of the head and those of carcinoma of the body and tail.

A review of 34 cases of carcinoma of the pancreas seen at the Graduate Hospital of the University of Pennsylvania and verified by laparotomy or necropsy justifies the following conclusions:

1. Carcinoma of the pancreas is a disease of fairly rapid progression (an average of six months from onset of symptoms to hospitalization) which occurs mostly in persons in the sixth and seventh decades (average age, 59.4 years) and affects mostly men (67.6 per cent) and white persons (73.5 per cent), although Negroes appear to be proportionately more prone to the disease than white persons (white persons:Negroes = 2.8:1, with an admission ratio of 3.5:1).

2. Pain is the outstanding chief complaint (in 64.7 per cent) and occurs at some time or other during the course of the disease more frequently (in 82.3 per cent) than does jaundice (70.5 per cent). Even in those cases in which the head of the pancreas is the dominant site involved pain will be present at some time during the course of observation just about as often as will jaundice (13 and 14 cases, respectively, in this series). When both jaundice and pain are present, the pain will precede the jaundice in approximately 85 per cent of cases. This was true in 90 per cent of our 10 cases in which the head was the dominant site of involvement.

3. The pain has no constant features common to a large majority but may be continuous and dull, paroxysmal or colicky; it is usually severe; it frequently radiates into the back and may be limited to the back; it is characteristically worse at night when a patient is lying down but is relieved by sitting up or walking about, and it may adopt an ulcer-like rhythm.

4. Although painless jaundice is a symptom complex of unquestionable diagnostic importance, it is not encountered with any great

frequency. One fourth (26.5 per cent) of all patients at the time of admission present painless jaundice, and it persists in one sixth (17.6 per cent) during the period of observation.

5. Whereas the head is nearly always invaded by the carcinomatous process when jaundice is present (20 out of 21 cases in which the parts affected could be determined), jaundice need not necessarily occur when the head is involved. In three tenths (10 out of 34, or 29.5 per cent) of all cases jaundice never developed, and in at least 60 per cent of these cases the head was definitely known to be involved.

6. Loss in weight is the most commonly noted symptom (90.1 per cent) and is usually rapid and severe. Weakness (78.3 per cent), nausea (47.8 per cent), vomiting (41.9 per cent) and anorexia (40.9 per cent) are associated symptoms which occur fairly frequently.

7. Constipation is found more often (43.3 per cent) than diarrhea (30 per cent). The ratio of occurrence of these symptoms (1.4:1), however, is much less than the usual ratio seen in routine office practice. Diarrhea, therefore, must be looked on as a symptom of some import in cases of suspected carcinoma of the pancreas.

8. The gallbladder can be felt on physical examination in four tenths (41.6 per cent) of those cases with associated jaundice and in one fourth (24.2 per cent) of all cases of carcinoma of the pancreas. Courvoisier's law is even more valuable to the surgeon at operation than to the clinician at the time of physical examination.

9. The liver is palpable in over three fourths (78.8 per cent), a pancreatic mass can be felt in one eighth (12.1 per cent) and ascites is demonstrable clinically in about one ninth (11.7 per cent) of all cases of a malignant condition of the pancreas in which the patient is seen in a hospital.

10. Some derangement of carbohydrate metabolism is an important diagnostic finding in cases of suspected pancreatic carcinoma. It may manifest itself in the form of an impaired dextrose tolerance curve (77.8 per cent), as hyperglycemia (27.3 per cent) or as glycosuria (24.2 per cent). All three of these defects could be demonstrated in one third (33.3 per cent) and either one of the three was found in four tenths (41.8 per cent) of all cases of carcinoma of the pancreas in this series.

11. Anemia (less than 4,500,000 red cells per cubic millimeter of blood) is seen in three fourths (75.8 per cent) of all cases but is strikingly mild (4,080,000 red cells and a hemoglobin concentration of 69.5 per cent as an average).

12. The roentgenogram is a most important adjunct in diagnosis. An initial diagnosis of a malignant condition in or about the pancreas

can be established by roentgen ray studies in almost one half the cases (45.2 per cent).

13. The determination of concentrations in the blood of such pancreatic enzymes as lipase and amylase offers a new diagnostic aid of real value. The concentration of serum lipase can be demonstrated to be abnormally great in over one third (36.1 per cent) of all cases prior to operation and in approximately 50 per cent at some time during the course of observation.

14. Occult blood in the stools can be demonstrated in one fourth (26.9 per cent) of all cases and its presence may be misleading when one is considering the differential diagnosis of this disease.

15. Fatty stools are uncommon (4 per cent).

It is necessary to revise the present concept of carcinoma of the pancreas. The major role of pain, the importance of demonstrating some impairment of carbohydrate metabolism and the value of the roentgenogram and of determinations of pancreatic enzyme concentration in the blood must be given due note. The traditional picture of painless jaundice and palpable distended gallbladder is seen in 25 to 40 per cent of cases and when present, of course, is significant, but unfortunately, in the majority of cases this syndrome is not presented. Fatty stools are rare.

SUMMARY

A poll was taken among 120 recent medically trained persons, representing thirty-four medical schools, on the question of their impressions of the outstanding diagnostic criterion of carcinoma of the pancreas. Jaundice was selected by 92.5 per cent (111) as the outstanding and commonest feature of the disease, and nearly half of this number specified further that the jaundice was painless. Only 2.5 per cent felt that pain ranked as the predominant characteristic.

An analysis was made of 34 cases of primary carcinoma of the pancreas proved by laparotomy or necropsy, and the results were combined with similar reviews previously reported in the literature.

Pain was shown to occur earlier and more frequently than jaundice and was the outstanding symptom. Painless jaundice proved to occur relatively infrequently.

Some derangement in carbohydrate metabolism, abnormalities in roentgenograms and elevated concentrations of pancreatic enzymes in the blood are findings of invaluable aid in the diagnosis of carcinoma of the pancreas.

In the combined analysis of our 34 cases and those already reported in the literature the following general features of the incidence of

carcinoma of the pancreas were noted: average age 56.4 years; men 71.3 per cent, with a ratio of men to women of 2.4:1; white persons 71.4 per cent, with a ratio of white persons to Negroes of 2.5:1; average duration of symptoms from onset to hospitalization six months, and average duration of illness from onset to death seven and one-tenth months.

In the same analysis the signs and symptoms of carcinoma of the pancreas occurred with the following frequencies:

Symptom	Occurrence, Percentage
Pain as an initial symptom	49.8
Pain as a chief complaint	48.5
Pain at some time during the course of the disease.....	76.4
Jaundice as an initial symptom	21.8
Jaundice as a chief complaint	30.5
Jaundice at some time during the course of the disease.....	68.8
Painless jaundice at the time of admission to the hospital.....	17.6
Painless jaundice throughout the course of observation.....	13.8
Loss of weight, with an average loss of 26.4 pounds (11.9 Kg.), and an average rate of loss of 6.8 pounds (3.1 Kg.) per week.....	87.4
Fatigue and weakness	51.1
Anorexia	44.4
Nausea and/or vomiting	42.3
Constipation	38.7
Diarrhea	10.8

Physical Finding	Occurrence, Percentage
Palpable liver	63.2
Palpable, distended gallbladder with associated jaundice.....	50.9
Palpable distended gallbladder, all cases.....	37.5
Palpable pancreatic mass	37.3
Ascites occurring preoperatively or antemortem	15.6
Ascites, all cases	23.7

Laboratory Finding	Occurrence, Percentage
Glycosuria	9.4
Hyperglycemia	19.4
Impaired dextrose tolerance	20.8
Anemia with an average red cell count of 4,010,000 and an average hemoglobin concentration of 75.7 per cent.....	32.4
Positive roentgenologic signs	37.0
Hyperlipasemia	40.0-60.0
Bloody stools	27.5
Fatty stools	9.7

Dr. Henry L. Bockus, professor of gastroenterology, Graduate School of Medicine, University of Pennsylvania, gave advice and criticism during this study.

PRIMARY PULMONARY VASCULAR SCLEROSIS

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Primary pulmonary vascular sclerosis in the restricted sense of the term defined by Brenner¹ is a rare condition. Up to 1935 Brenner collected from the literature only 15 cases, to which he added 1 of his own. This number, however, is probably incomplete; at least 1 other case should be included, the one reported by MacCallum.²

Since 1935 2 additional instances have been reported; including the case herein presented, there are now on record some 20 cases fulfilling the requirements for inclusion within this restricted group.

These requirements are (1) the presence of significant hypertrophy of the right ventricle but not of the left and (2) the absence of all factors commonly believed to cause secondary pulmonary vascular sclerosis, pulmonary hypertension or isolated strain of the right side of the heart.

REPORT OF A CASE

A married woman aged 21 entered the Multnomah County Hospital Feb. 2, 1940 because of dyspnea and pain in the chest. She had been moderately short of breath on exertion "all her life," but during the last two years dyspnea became increasingly severe and for the past several months she experienced paroxysms of dyspnea and orthopnea even while at rest, especially at night.

Although she had been told by a physician that she was a "blue baby" at birth and was under the impression that she had always had "heart trouble," no evidence of congenital or any other heart disease was noted on numerous observations in this clinic prior to September 1938, only a little more than one year before her death. Her first appearance at the clinic was in 1931, when she was 12 years of age. Her complaint then was of a "sore throat," and a general examination revealed large tonsils and adenoids. The heart was recorded as normal. Between 1931 and 1938 she was seen on numerous occasions for various and sundry conditions, including pregnancy in 1936, when she was delivered of a healthy baby after a normal, uneventful period of gestation. Many of these observations included

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1. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, *Arch. Int. Med.* **56**:976-1014 (Nov.) 1935.

2. MacCallum, W. G.: Obliterative Pulmonary Arteriosclerosis, *Bull. Johns Hopkins Hosp.* **49**:37-48 (July) 1931.

complete physical examinations, and, with the exception of one notation concerning "substernal pulsations," the heart was invariably described as normal; the statement "no murmurs heard" often appeared on the record.

In September 1938, one year and four months before her final admission, she entered the hospital because of dyspnea, vomiting, headache and hemoptysis, and for the first time the question of congenital heart disease came up for consideration. At that time the following significant history was elicited: On slight exertion she often suffered severe dyspnea, cyanosis, precordial pain without radiation, dizziness and fainting spells. She had several attacks of hemoptysis but no cough. She had had scarlet fever at the age of 4 but gave no history of rheumatic fever.

Examination revealed cyanosis, "widening of the heart" with "filling of the waist" and a markedly accentuated pulmonic second sound. Largely on these find-

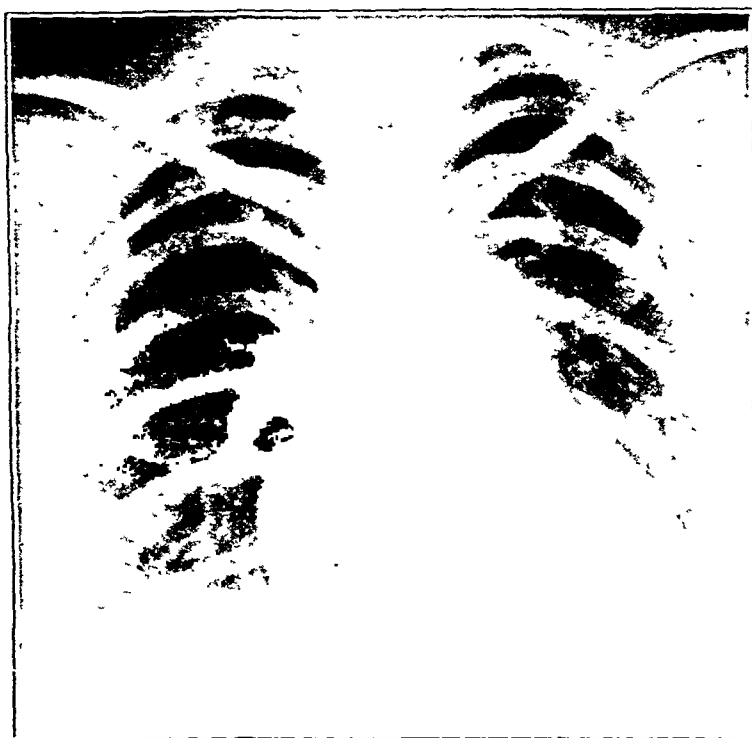


Fig. 1.—Roentgenogram taken nine days before death, showing marked dilatation of the pulmonary artery and conus.

ings, together with roentgenographic evidence of a prominent pulmonary conus, a diagnosis of congenital heart disease was seriously considered, although no murmurs of any sort were heard. Despite the dyspnea, clear lung fields were found on both physical and roentgen examination. It was also noted that there was "no increase in venous pressure." The arterial pressure was 85 systolic and 70 diastolic and was "difficult to get." The basal metabolic rate was -14 per cent. Examination of the blood showed the hemoglobin concentration was 122 per cent, the erythrocyte count 5,700,000 and the leukocyte count 17,550, with 68 per cent neutrophils. The erythrocyte sedimentation rate was 1 mm. for fifteen minutes and 3 mm. for forty-five minutes. The Wassermann, Kahn and Klein reactions were all negative.

The electrocardiogram disclosed the following changes indicative of pronounced right ventricular strain: namely, marked right axis deviation; tall and sharply

spiked P waves, especially in lead II; inversion of the T wave in lead III, and inversion of the T wave without inversion of the QRS complex in lead IV.

The patient's final admission to the hospital was on Feb. 2, 1940. During the preceding year she was under more or less continuous observation in the outpatient department. She complained of increasing dyspnea, palpitation, precordial pain, headache, dizziness, vertigo, fainting spells and attacks of nausea and vomiting. Slight edema of the ankles had developed during the previous two or three months.

Examination at this time disclosed diffuse cyanosis of the face and lips, with malar flush, and deep cyanosis of the nail beds. The heart appeared moderately

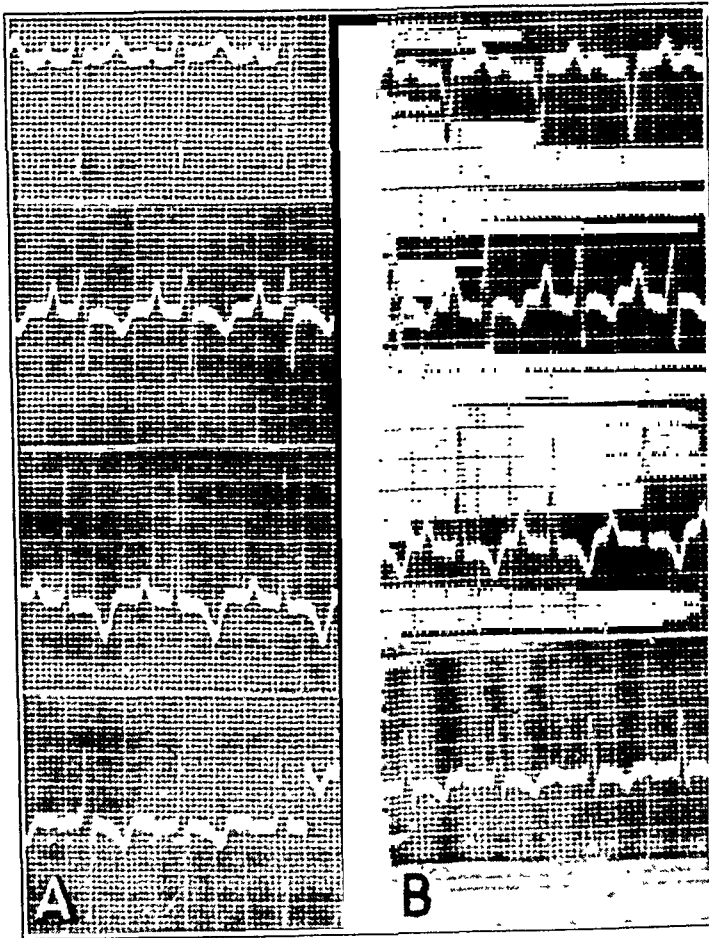


Fig. 2.—Electrocardiograms taken (A) September 1938 and (B) February 1940, showing marked right axis deviation, tall and sharply spiked P waves and inversion of the T waves in leads II, III and IV, without inversion of the QRS complex in lead IV.

enlarged, with a strong, forceful apex beat about 11 cm. to the left of the mid-sternal line. The pulmonic second sound was greatly accentuated, but there were no murmurs. The blood pressure was 90 systolic and 75 diastolic. The lung fields were clear throughout. The liver was just palpable below the costal margin, and there was no dependent edema. The roentgenogram of the chest confirmed the clearness of the lung fields and the moderate cardiac enlargement noted clinically. It also disclosed extreme prominence of the pulmonary artery and conus. The

electrocardiographic tracings, the blood counts and other laboratory data were essentially like those previously described.

Clinical Diagnosis.—When the history as just related was presented on Feb. 8, 1940, at one of the regular medical conferences, it appeared clear that the clinical picture was one of severe isolated right-sided heart strain, or primary cor pulmonale. It was also evident from the physical and roentgenologic examinations that no ordinary pathologic condition of the lungs, such as emphysema or pulmonary fibrosis, existed to account for such strain. Mitral stenosis was excluded



Fig. 3.—Anterior view of the heart. The arrow (*A*) indicates the lateral boundaries of the right ventricle. The anterior incision passes through the right ventricle and the center of the pulmonary conus. The entire apex is formed by the right ventricle. Note the small size of the left ventricle (*B*) as compared to that of the right ventricle (*A*) and the striking difference between the right atrial appendage (*C*) and the left atrial appendage (*D*).

with reasonable certainty by the absence of pulmonary engorgement and by the roentgenographic demonstration of a small left auricle. Furthermore, the complete absence of murmurs and thrills and the normal cardiac findings recorded in the numerous observations prior to September 1938 furnished ample evidence against congenital cardiac disease. Because of these considerations a diagnosis was made of primary pulmonary vascular sclerosis.



Fig. 4.—Heart opened to show the relative size of the cardiac chambers. The hypertrophy and dilatation of the right ventricle (*A*) and the lack of corresponding change in the left ventricle (*B*) are readily apparent.



Fig. 5.—A small pulmonary artery (*A*) showing a canalized thrombus.

Four days later, during which interval her condition had remained essentially unchanged, the patient died suddenly.

Gross Postmortem Examination.—The body was that of a well developed and well nourished white woman. Slight cyanosis was apparent in the nail beds and the lips. The chest was symmetric. There was no edema.

The abdominal cavity contained between 100 and 200 cc. of free serosanguineous fluid; the peritoneal surfaces were smooth and shiny. The liver extended 5 cm. below the xiphoid process. The spleen did not extend below the costal margin. No abnormalities were noted in the gastrointestinal tract.

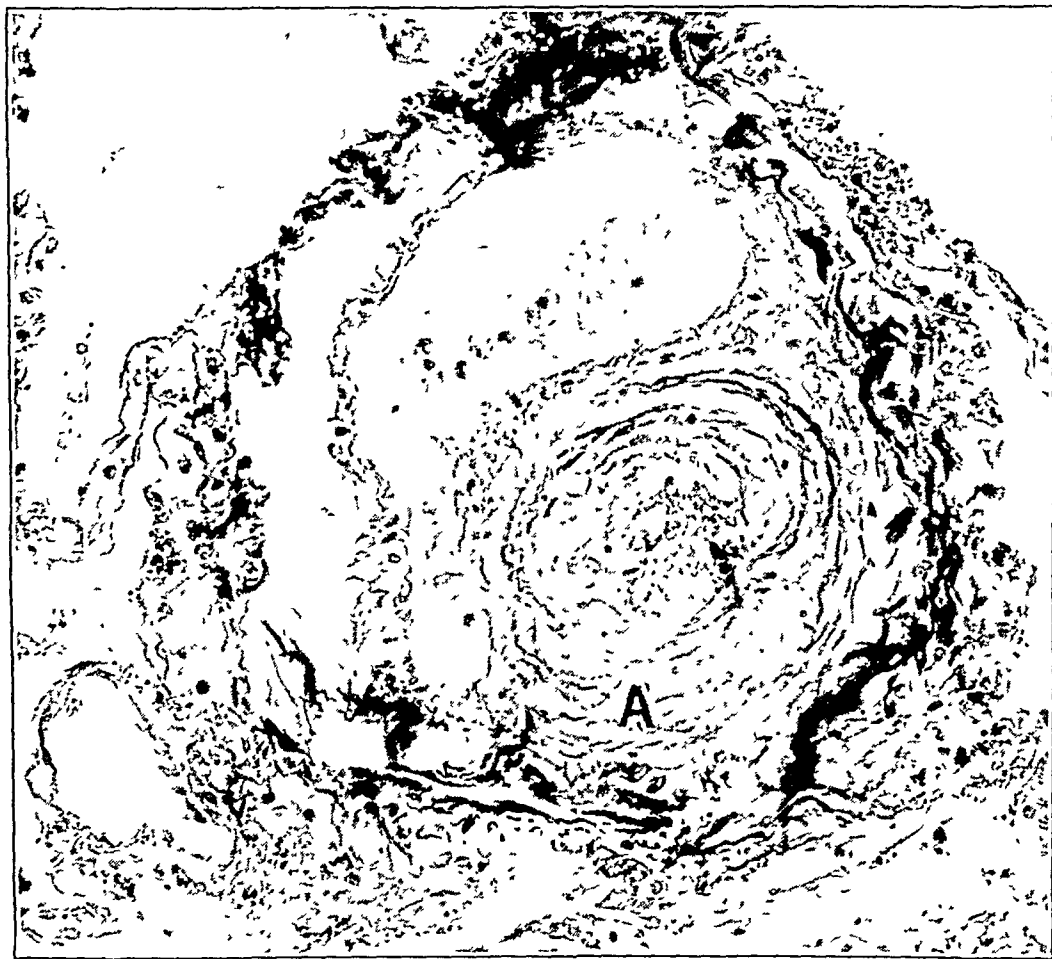


Fig. 6.—A small pulmonary artery (A) which has been the seat of a proliferative intimal change, with narrowing of the lumen and subsequent occlusion.

There was no fluid in either pleural cavity. The lungs were pinkish, voluminous and crepitant. The bronchi were dissected and opened as far as the tertiary branches and were found to be normal. On section the pulmonary parenchyma appeared homogeneous; no consolidations or other gross abnormalities were seen. The pulmonary arteries were dissected as far as the tertiary branches; the formation of occasional atherosclerotic plaques was noted.

The pericardial sac contained only a few cubic centimeters of free clear yellow fluid and presented a smooth, shiny inner surface. The heart was enlarged; the maximum transverse diameter was 13 cm., and the weight was 690 Gm. The

enlargement and increased weight were due entirely to dilatation and hypertrophy of the right auricle and ventricle. The left chambers were distinctly small. The size of the right ventricle was more than twice that of the left, and the right auricle was about six times as large as the corresponding left chamber. The myocardium of the right ventricle at the tip and the base measured, respectively, 7.5 and 7 mm. in thickness; the corresponding regions in the left ventricle measured 7 mm. each. The pulmonary artery and conus were extremely prominent. The circumference of the pulmonary valve measured 8.5 cm. and that of the aortic valve 6 cm.; the tricuspid valve measured 12 cm. and the mitral valve 10 cm.

No congenital cardiac defects were present; the foramen ovale was anatomically patent but functionally closed. The coronary vessels were free from sclerosis.

The eviscerated thoracic cage presented no deformities. The aorta was small; it was opened throughout its entire length, and no sclerosis or other changes were found.

The liver was moderately enlarged and was the seat of mild passive congestion. All other abdominal and pelvic organs were essentially normal.

Microscopic Postmortem Examination.—The only significant changes concerned the pulmonary vessels. The lung parenchyma proper presented no abnormalities. The most striking changes were found in the arterioles and capillaries. The majority of the arterioles presented intimal proliferation, which resulted in marked narrowing or complete occlusion of the lumens. The muscularis showed no corresponding hypertrophy. In many of the small arterioles there were present thrombi of various ages. In some instances recanalization had occurred. Many of the capillaries were completely obliterated and hyalinized. The extent of the arteriolocapillary obliteration was such as to indicate a high degree of obstruction within the pulmonary circuit. The larger and medium-sized arteries showed no changes other than the formation of occasional atherosclerotic plaques.

Sections of the liver showed slight dilatation of the venous sinuses and slight swelling of the liver cells.

Sections of the spleen, kidneys and adrenal glands showed no abnormalities.

No significant sclerosis was present in any of the systemic vessels examined.

Comment.—This case in the highest degree fulfils the requirements for a diagnosis of primary pulmonary vascular sclerosis. The outstanding clinical picture was that of severe right-sided heart strain, resulting in death; pathologically marked isolated cor pulmonale was present, and the sole lesion which might bear a causative relation to this fatal cor pulmonale was extensive sclerosis and occlusion of the pulmonary vascular tree. No other possible known cause of right-sided heart strain was present, even in the slightest degree.

The mechanism of death merits comment. Only slight evidence of congestive heart failure was noted either clinically or pathologically. However, more than a year prior to death the patient, while yet under 20 years of age, began to suffer attacks of precordial pain. Sometimes the pain was described as "not radiating," and the attacks were often associated with cyanosis. This association suggests similarity to the "hypercyanotic angina" which has been described, especially by the older writers on so-called Ayerza's disease, as occurring occasionally in severe

grades of chronic cor pulmonale. Although pathologically the coronary vessels were patent and singularly free of sclerosis, it appears highly probable that the final event of sudden death as well as the earlier attacks of anginal pain was due to acute coronary insufficiency arising from a greatly diminished volume of blood delivered to the left ventricle through the obstructed pulmonary circulation. The probable mechanism involved in this type of death was discussed in an earlier communication³ describing a case of "subacute cor pulmonale" in which a similar death occurred.

SUMMARY OF PREVIOUSLY REPORTED CASES

CASE 1 (Mönckeberg⁴).—A woman aged 33 complained of nervousness and anemia. Examination revealed an enlarged heart, with a systolic and a diastolic murmur over the apex and a systolic murmur over the base, more prominent over the pulmonic area. The blood pressure was 125 systolic. Death occurred after four months with signs of increasing heart weakness. At autopsy there was found pronounced widening of both primary branches of the pulmonary artery. The heart was distinctly enlarged, chiefly because of hypertrophy of the right chambers. The left ventricle appeared as an appendage to the right one.

Microscopically there was sclerosis of the pulmonary arteries, which became diffuse in the branches of the second and third order. In the small branches the intima was four times the thickness of the media. The lung parenchyma was normal.

CASE 2 (Rössle⁵).—Increasing dyspnea and palpitation developed in a woman aged 20. Death occurred at the end of two years. An antemortem diagnosis of congenital heart disease was made.

At autopsy the large branches of the pulmonary artery showed no change, but all the branches with a diameter of 0.5 to 0.4 cm. revealed many yellowish nodules and plaques. There were enormous hypertrophy and dilatation of the right cardiac chambers. The left side of the heart appeared as a mere appendage of the right. No valvular or other structural lesions were present.

Microscopic examination disclosed newly laid down, fine elastic elements in the arteries. The thickened intima in the middle-sized vessels was distinctly fatty in character. The lung parenchyma was normal.

CASE 3 (Sanders⁶).—No clinical findings or impressions were reported. At necropsy the smaller branches of the pulmonary artery were considerably stiffer and thicker than normal. The right ventricle was enormously hypertrophied.

Microscopically the branches of the pulmonary artery 4 to 5 mm. in diameter showed the intima to be thicker than the media. This was due to an increase in connective tissue and in the elastic elements. The lung parenchyma showed no significant change.

3. Brill, I. C., and Robertson, T. D.: Subacute Cor Pulmonale, *Arch. Int. Med.* **60**:1043-1057 (Dec.) 1937.

4. Mönckeberg, J. G.: Ueber die genuine Arteriosklerose der Lungenarterie, *Deutsche med. Wchnschr.* **33**:1243-1246 (Aug. 1) 1907.

5. Rössle, R.: Ueber Hypertrophie und Organkorrelation, *München. med. Wchnschr.* **55**:377-381 (Feb. 25) 1908.

6. Sanders, W. E.: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, *Arch. Int. Med.* **3**:257-262 (April) 1909.

CASE 4 (Schütte⁷).—A woman aged 74 died with a condition diagnosed as cardiac insufficiency, with edema, ascites and pleural effusion. No detailed clinical history was given.

At autopsy the lungs were grossly normal. The heart was definitely enlarged. The right ventricle, especially the pulmonary conus, was greatly dilated and hypertrophied.

Microscopically the small branches of the pulmonary artery showed marked intimal thickening. No change was present in the larger vessels. There were generalized anasarca and hydropericardium.

CASE 5 (Ljungdahl⁸).—A woman aged 36 complained of shortness of breath and palpitation. After a few months there developed swelling of the abdomen, which was progressive and later became associated with swelling of the feet.

On physical examination she presented marked ascites but no peripheral edema while resting in bed. The heart was enlarged to the right and left, and forceful pulsation was seen and felt to the left of the lower part of the sternum. A systolic murmur was heard at the apex but was most intense in the third intercostal space. The pulmonary first sound was absent and was replaced by a loud systolic murmur; the second sound was soft and was accompanied by a rough diastolic murmur. A systolic murmur was also heard at the aortic area. There were pallor and slight cyanosis of the lips. A Talma operation was performed for the ascites, but the patient did not improve and died of progressive decompensation.

At postmortem examination the pulmonary veins were seen to be strikingly narrow. The pulmonary artery 8 cm. above the valve showed a thickened intima. In the main branches likewise there was a high grade sclerotic process with many cartilage-like plaques in the intima, resulting in narrowing of the vessels. Branches of the second and third order had a thin, delicate intima and were not grossly altered. The right auricle and right ventricle were extremely enlarged. The myocardium measured 8 mm. in thickness. The left ventricle was small and appeared as an appendage to the right. Its wall measured 11 to 12 mm. in thickness.

Microscopically the trunk and main stem arteries revealed hyperplasia of the connective tissue of the intima, with no elastic tissue but many fat globules. The thickness of the connective tissue varied from 0.32 to 0.88 mm. This change was confined to the trunk and main branches; no changes were found in the smaller branches.

Other findings included ascites and chronic passive congestion.

CASE 6 (Hart⁹).—A woman aged 30 was admitted to the hospital with high grade cyanosis, severe dyspnea and a laboring heart, with murmur.

At necropsy the lungs were grossly normal. The main stem of the pulmonary artery was almost twice as wide as the aorta, but the walls were not thickened. Raised yellow plaques were present on the intima, with wrinkling in between; there were also single, split pea-sized places which were calcified. In the branches

7. Schütte, H.: Rechtsseitige Herzhypertrophie hervorgerufen durch eine entzündliche Veränderungen der kleinen Lungenarterien, *Centralbl. f. allg. Path. u. path. Anat.* **25**:483-485, 1914.

8. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915.

9. Hart, C.: Ueber die isolierte Sklerose der Pulmonalarterie, *Berl. klin. Wchnschr.* **53**:304-306 (March 20) 1916.

the intima showed many yellowish white flecks, with raised furrows between. A spreading adherent thrombus was found in the right pulmonary artery. The heart was approximately twice the normal size, chiefly because of enlargement of the right chambers. The apex was formed by the right ventricle. The pulmonary conus was greatly hypertrophied.

CASE 7 (Hart⁹).—A woman aged 25 had been under a physician's care for a cardiac condition for six months. After this period she was bedridden for three weeks, with marked dyspnea, cyanosis and forceful pounding of her heart.

On physical examination she presented cyanosis, edema of the ankles, pulsating, distended jugular veins and a thrill over the apex of the heart. Systolic and diastolic murmurs were heard over the apical and pulmonary areas. The radial pulse was small, and its rate was slow. She died suddenly.

At autopsy the pulmonary artery and branches were of normal width; in the smaller vessels the intima had yellowish white plaques. There was hypertrophy of the right ventricle and atrium with atrophy of the left ventricle. The apex of the heart was formed by the right ventricle.

In this case, as in the preceding one (case 6), no detailed microscopic observations were given, but in the discussion the author implied that significant microscopic changes were present.

CASE 8 (Krutzsch¹⁰).—A man aged 26, for whom no clinical history was included, was found at autopsy to have lungs of deep brown color, with edema and atelectasis at the bases. The main stem of the pulmonary artery had a smooth intima, except for occasional thickening. The branches of the first order were corrugated and showed fine thickenings. There were striking thickenings in the branches of the second and third order and in the smaller branches.

The heart was greatly enlarged, chiefly because of hypertrophy and dilatation of the right ventricle. The myocardium of the right ventricle was 12 mm. thick at the conus. The wall of the left ventricle was 11 mm. thick. The circumference of the pulmonary artery was 8 cm., of the aorta 6.5 cm. and of the tricuspid valve 14 cm.

Microscopically the arteries and arterioles showed a thickened intima, composed of loose, fine connective tissue with some proliferation of the elastic tissue. There were numerous lymphocytes in some and occasional strands of hyaline connective tissue in others. Fat droplets were present in some areas of thickening.

Other findings included anasarca, cyanosis of the face, hydropericardium and chronic passive congestion of the liver, spleen and kidneys.

CASE 9 (Krutzsch¹⁰).—A man aged 23, for whom no clinical history was available, was found at necropsy to have sharply circumscribed reddish brown areas which stood out above the surface in the lower lobes of both lungs. The larger pulmonary vessels showed yellowish thickenings of the intima. In the medium-sized arteries there were plaques of confluent character; in the smaller branches there were many more such plaques.

The heart was greatly enlarged, because of great increase in size of the right ventricle; the left ventricle appeared merely as an appendage. The wall of the right ventricle measured 9 mm. in thickness at the conus; the wall of the left one

10. Krutzsch, G.: Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, Frankfurt. Ztschr. f. Path. 23:247-271, 1920.

measured 10 mm. in thickness. The circumference of the aorta was 7 cm., of the pulmonary artery 8 cm., of the mitral valve 11 cm. and of the tricuspid valve 14 cm.

Microscopic lesions were apparently identical with those described in case 8; the one description was given by the author as applicable in both cases.

Other findings included cyanosis of the face, hands and finger nails and chronic passive congestion of the viscera.

CASE 10 (Eppinger and Wagner¹¹).—A man aged 50 complained of swelling of the lower extremities, shortness of breath, anorexia, hoarseness and fulness of the neck. These symptoms were of one year's duration; one month before death there developed edema and cough.

On physical examination there were found cyanosis, distention of the veins of the neck, edema of the dependent portions, slight dyspnea, hoarseness, signs of atelectasis at the bases of the lungs, enlargement of the heart on percussion with accentuated pulmonic sounds, ascites and an enlarged, pulsating liver. The roentgenogram and electrocardiogram showed hypertrophy of the right side of the heart. The red blood cell count was 6,320,000.

A diagnosis was made of primary vascular disease of the pulmonary artery.

At autopsy the lungs were compressed focally. They were deeply pigmented. The pulmonary artery and all its branches were grossly normal. The right side of the heart was enlarged to twice the normal size; the left ventricle was small. The thickness of the wall of the left ventricle was scarcely 1 cm.; that of the wall of the right ventricle was more than 1 cm.

Microscopically there was marked thickening of the smallest vessels. The intima was thickened in a plaquelike manner, which resulted in some areas in complete occlusion. The changes were diffuse.

Other findings included general cyanosis, anasarca, chronic passive congestion of the viscera and a broadened, flabby, thin-walled aorta.

CASE 11 (Tschistowitsch¹²).—A woman aged 38, whose chief complaints were of edema of the feet and dyspnea, was found on physical examination to have pronounced hypertrophy of the right side of the heart, intense cyanosis, edema of the feet and dyspnea. There were no other cardiac signs. A diagnosis was made of "pulmonary arteriosclerosis with marked emphysema." She died in two months, without responding to the administration of heart-stimulating drugs.

At autopsy the lungs were normal, with no gross sclerosis of the pulmonary arteries. There was pronounced hypertrophy of the right side of the heart.

Microscopically marked intimal thickening of the small arteries, with thrombosis in many, was apparent. Many arteries were completely occluded, as were many of the capillaries.

CASES 12 and 13 (Goedel¹³).—Two men aged 59 and 50, respectively, entered the hospital, each with a picture of rapidly developing heart failure. They

11. Eppinger, H., and Wagner, R.: *Zur Pathologie der Lunge*, Wien. Arch. f. inn. Med. **156**:83-146, 1920.

12. Tschistowitsch, T.: *Thrombo-endoartérite pulmonaire chronique*, Compt. rend. Soc. de biol. **89**:627, 1923.

13. Goedel, A.: *Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie*, Virchows Arch. f. path. Anat. **277**:507-521, 1930.

presented dyspnea, marked cyanosis and distressing cough, but no edema. In both the condition was diagnosed as "myocardial degeneration."

At autopsy in each instance there were marked enlargement and dilatation of the right ventricle. The left side of the heart appeared atrophic. The valves were intact. In the first case the lungs were congested and slightly edematous. There was a thrombus in the main stem of the pulmonary artery, which continued through both main branches into the middle-sized arteries, occluding many. Microscopically the thrombus was old and partially organized. There were areas of thickening of the intima with partially hyalinized connective tissue. The terminal arteries revealed intimal hyperplasia, with thrombus formation and often recanalization.

In the second case the lungs were congested but not edematous. An occasional middle-sized artery was occluded by thrombosis. A slight amount of lipid flecking and streaking was also seen in the intima.

Microscopically the small arteries showed the most change, which consisted of intimal proliferation with narrowing of the lumen, thrombus formation and recanalization. There were injected capillary-like vessels in the periadventitia, in the peribronchial tissue and in the bronchial submucosa.

CASE 14 (MacCallum²).—A Negro housewife aged 39 complained of pain in the stomach and shortness of breath. At 24 she began to be breathless on exertion. One year later she began to have fainting attacks, always associated with undue physical exertion. One year ago, at 38 years of age, when she was hospitalized for an operation on the uterus, her heart seemed normal except for a systolic murmur to the left of the sternum and an accentuated second pulmonic sound. Four months ago the old symptoms, including cough and tightness about her heart, returned, with increased severity.

Examination revealed a temperature of 100 F., a pulse rate of 125 per minute, a respiratory rate of 24 per minute, a blood pressure of 125 systolic and 95 diastolic, dyspnea, moderate cyanosis and enlarged, pulsating neck veins. The lungs were normal. The heart was much enlarged to the right and to the left; sounds were loud, especially the pulmonic second sound; a marked presystolic gallop, a loud first sound, a soft systolic murmur and a faint mid-diastolic murmur were heard at the apex. There was slight edema of the extremities. The Wassermann reaction of the blood was negative. The electrocardiogram showed pronounced right axis deviation. The heart grew progressively weaker. Finally, with nausea, dyspnea, delirium and pain in the chest and the epigastrium, she lost consciousness and died.

At autopsy there were found arteriosclerosis and arteriolosclerosis of the pulmonary arteries, with secondary thrombosis and organization of the thrombi. The formation of plaques and the thickening were limited to the intima; the media and adventitia were fairly normal. While all the pulmonary arteries were involved, the process was most marked in those arterioles which measured much less than 1 mm. in diameter.

The heart was greatly enlarged, wholly because of hypertrophy and dilatation of the right auricle and ventricle. No valvular or other structural defects were seen.

The lung tissue in general was surprisingly free from disease.

CASE 15 (Kuntschik¹⁴).—A 15 year old girl, whose chief complaint was hemoptysis, had suffered with heart trouble for the previous ten or eleven years and

14. Kuntschik, R.: Zur Kenntnis der sogenannten primären Pulmonalsklerose, *Ztschr. f. Kreislaufforsch.* **23**:183-198 (March 15) 1931.

had been unable to do heavy work. She was feeble, listless and often short of breath, but the dyspnea was never of a high grade. Fever and bloody sputum developed a week before she was hospitalized. She was thought to have tuberculosis and was put to bed, but the cultures of the sputum, which continued to be blood tinged, were negative for tubercle bacilli. Cough, cyanosis and tachycardia continued. Death was sudden.

At autopsy the lungs were somewhat collapsed, and the lower lobe of the left lung contained an infarct. In the branches of the main pulmonary artery and in the secondary vessels there were raised, yellowish white atherosclerotic lesions. Marked narrowing was present in the medium and small vessels. The heart was enlarged, and the apex was formed by the right ventricle. The left ventricle appeared as an appendage to the right. The right ventricular wall measured 14 mm. in thickness and the left ventricular wall 7 mm. The circumference of the pulmonary artery was 58 mm. and that of the aorta 42 mm.

Microscopically the vessels of the second and third order had an intimal thickening which was two or three times the thickness of the media and was formed by loose, cellular connective tissue. In the smallest branches all parts of the walls were thickened, especially the intima, which resulted in marked narrowing and often complete occlusion of the lumens. Fresh thrombi were found here. There was proliferation of connective tissue around the blood vessels.

Other findings included cyanosis of the lips and face, stasis of the abdominal viscera and caseous tuberculosis of the right adrenal gland.

CASE 16 (Ulrich¹⁵).—In a 31 year old woman, who had suffered hoarseness and amenorrhea for two years, there developed swelling of the feet, ankles and abdomen six months before death. Occasionally blood-streaked sputum occurred.

On physical examination she presented congestive failure with more cyanosis than usual, but with no evidence of moisture at the bases of the lungs. A visible and palpable pulsation was present in the interscapular area (third spinous process), and here a marked systolic bruit could be heard. Roentgen examination revealed a prominent pulmonary bulge and enormously dilated pulmonary arteries at the hilus, the pulsations of which were visible under the fluoroscope. Right axis deviation was present in the electrocardiogram. The hemoglobin concentration and red blood cell count were increased.

At autopsy the pulmonary artery was seen to be extensively dilated, and its branches showed an extreme amount of yellow raised intimal thickening. The right ventricle showed extreme hypertrophy and dilatation.

Microscopically there was seen appreciable intimal thickening in the small arteries, proliferative in character. In many of the small vessels the lumens were almost completely occluded. A marked atheromatous condition was present in the larger vessels.

Other findings included signs of congestive failure.

CASE 17 (Brenner¹).—In a boy aged 11 dyspnea and dizziness developed. On physical examination the heart was not found to be enlarged. A pulmonary systolic murmur and an accentuated pulmonic second sound were present. The roentgen ray examination revealed a normal-sized heart with a prominent pulmonary artery; the electrocardiogram disclosed right axis deviation.

In the next two years there developed syncopal attacks, with drowsiness, cyanosis, muscular rigidity and incontinence, followed by vomiting. Dyspnea and

15. Ulrich, H. L.: The Clinical Diagnosis of Pulmonary Arteriosclerosis, *Ann. Int. Med.* 6:632-644 (Nov.) 1932.

cyanosis continued to increase, and attacks of precordial pain developed. He had at this time a heart slightly enlarged as determined by physical examination, with a harsh systolic pulmonic murmur, an accentuated P wave in lead II and an occasional diastolic pulmonic murmur. The roentgen examination revealed marked prominence and increased pulsation of the pulmonary artery and hilar shadows. The electrocardiogram again revealed right axis deviation. He died suddenly, during an attack of precordial pain.

At necropsy there were noted congestion and edema of the lower lobes of the lungs. The stem and main branches of the pulmonary artery had a thickened wall and a thickened and pitted intima; a few atherosclerotic patches were seen. The heart was enlarged and markedly dilated, with great hypertrophy of the right ventricle. The right auricle was not dilated or hypertrophied.

Microscopically slight sclerosis of the stem of the pulmonary artery and thickening of the media were seen. Many of the small arteries presented intimal proliferation with great narrowing of the lumens. Some had proliferation of the elastica interna; others showed hypertrophy of the media. The lung parenchyma presented no significant changes.

CASE 18 (Mallory¹⁶).—A boy aged 10 years complained of dyspnea on exertion with cyanosis for two years and swelling of the legs for eight months preceding his admission to the hospital. He was unable to lie flat in bed and had nocturia and emesis.

Physical examination showed dyspnea, cyanosis of the lips and a barrel-shaped chest with bulging of the precordium. Rales were present at the bases of both lungs, and breath tones were diminished to absent. The veins of the neck were enlarged and pulsating. The heart was enlarged to the right and left, and a pre-systolic gallop rhythm was heard over the entire precordium. The electrocardiogram revealed right axis deviation, an inverted T wave in lead III, high P waves in leads I and II and a depressed ST interval in lead II. The roentgen examination showed the heart enlarged to the right, with increased density at the bases of the lungs.

Death was due to progressive decompensation.

At autopsy the lungs were heavy and less crepitant than normal. A small pulmonary infarct was present. The right ventricle was greatly hypertrophied and dilated. The left and the right auricle were considerably dilated. The left ventricle was normal. Fibrous thickenings almost as thick as the muscle, with focal calcification, were present in the left auricle.

Microscopically an obliterative process was seen in the majority of the smaller vessels, the veins as well as the arteries. There was internal thickening in some of the larger veins (possibly related to the process in the auricle). The alveolar walls were thicker than normal, and dilatation of the lymphatics was seen. A few areas of scarring were present.

CASE 19 (Killingsworth and Gibson¹⁷).—A boy aged 10 complained of attacks of unconsciousness which came on while playing, preceded by choking and inability to breathe. During these attacks the skin became blue and the extremities cold.

16. Cor Pulmonale, Etiology Unknown, Cabot Case 23511, *New England J. Med.* **217**:1045-1049 (Dec. 23) 1937.

17. Killingsworth, W. P., and Gibson, S.: Primary Proliferative Pulmonary Arteriolar Sclerosis, *Am. J. Dis. Child.* **57**:1099-1109 (May) 1939.

The pertinent physical findings included an enlarged heart in gallop rhythm, a thrill and a diastolic murmur at the pulmonary area and a blood pressure of 84 systolic and 72 diastolic; the liver edge was palpable $1\frac{1}{2}$ inches (3.8 cm.) below the costal margin. Roentgen examination disclosed slight cardiac enlargement with extreme prominence of the pulmonary conus. The electrocardiogram revealed right axis deviation. Death was sudden.

At autopsy there were small focal atelectatic areas in the basilar portions of both lungs and dilatation of the pulmonary arterial system. The right ventricle and right auricle were markedly dilated.

Microscopically the pulmonary vessels 1 to 2 cm. in diameter showed moderate proliferation in the intima and slight change in the media. Vessels smaller than 1 cm. in diameter showed marked intimal proliferation, resulting in many instances in complete occlusion.

Comment.—As already stated, the 20 cases the histories of which have just been chronicled probably do not constitute a complete list of those that may qualify for inclusion in the restricted group under discussion. However, it does appear that the majority of the 100 or more cases which are now recorded in the literature under the title of primary pulmonary arteriolar or vascular sclerosis may be excluded, because their records indicate that some pathologic process (pulmonary, pleural, cardiac, etc.) in addition to the pulmonary vascular disease was present which might have been responsible for strain of the right side of the heart. On the other hand, some cases, such as the one reported by Seely,¹⁸ probably should be included, for although "pulmonary emphysema" was mentioned in the anatomic diagnosis, the amount of emphysema indicated by the description of the lungs was so slight as to be practically negligible as a factor in the production of strain of the right ventricle.

An interesting and puzzling group of cases are those in which there is a clinical picture of severe primary cor pulmonale but in which at autopsy there is no evidence of any lesion whatever, either in the pulmonary vessels or elsewhere, to account for the marked hypertrophy of the right side of the heart. Striking examples are case II of Ulrich¹⁵ and some of the cases reported recently by East¹⁹ and by de Navasquez, Forbes and Holling.²⁰ The latter authors, impressed with the total absence in their cases of a cause for the right-sided heart strain, questioned the significance of the pulmonary vascular lesions in all other cases; they proposed the abandonment of the term "primary pulmonary vascular sclerosis" and suggested in its place the term "idiopathic right ventricular hypertrophy."²¹ East¹⁹ preferred the designation of "pulmonary hypertension."

ANALYSIS OF SIGNS AND SYMPTOMS

Both sexes were represented evenly.

The ages varied from 10 to 74, but in only 4 cases were the patients 50 or over, and in 14 cases they were under 40.

18. Seely, H.: Primary Obliterative Pulmonary Arteriolar Sclerosis, *J. A. M. A.* **110**:792-794 (March 12) 1938.

19. East, T.: Pulmonary Hypertension, *Brit. Heart J.* **2**:189-200 (July) 1940.

20. de Navasquez, S.; Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-Called Pulmonary Hypertension, *Brit. Heart J.* **2**:177-188 (July) 1940.

21. Perhaps a better term would be "idiopathic cor pulmonale," which would indicate changes in the right auricle as well as in the right ventricle.

The most important sign, one present in all cases, is the roentgenographic demonstration of enlargement, dilatation or prominence of the pulmonary artery and conus. As a corollary to this, although not so universally constant, is the electrocardiographic demonstration of pronounced right axis deviation, along with other alterations in the auricular and ventricular complexes indicating an extreme degree of cor pulmonale.

Dyspnea was present in 14 of the 20 cases reviewed. Orthopnea was present in 4. Cyanosis of varying degree was noted in 14 and palpitation in 5. Fainting spells were present in 3, pain in the chest or anginal pain in 4, vomiting in 5, dizziness in 5, hemoptysis in 3 and cough in 4. Cardiac murmurs were noted in 7 and thrills in 2. Other symptoms occurring occasionally were headache, anorexia, somnolence, hoarseness, anemia, fever and tightness about the chest.

Congestive failure, affecting the systemic venous system, varying in degree from slight to extreme, occurred in most of the cases; congestion or edema of the lung was comparatively infrequent. Pulmonary atelectasis was noted more often.

Readings of the blood pressure were available in only 4 of the 20 cases. They were: 125 systolic and 95 diastolic; 125 systolic; 90 systolic and 75 diastolic, and 84 systolic and 75 diastolic. The venous pressure was elevated in most of the cases.

Death occurred suddenly in 5 instances.

In 2 of the 20 cases the condition was correctly diagnosed during life.

DIAGNOSIS

An examination of the signs and symptoms just described indicates that they do not differ in any essential respect from those which occur in other types of cor pulmonale secondary to cardiopulmonary disease. The diagnosis therefore depends on the following factors: (1) the demonstration (especially by roentgenographic and electrocardiographic means) of the existence of pronounced strain of the right ventricle *but not of the left*, and (2) the exclusion, by every available means, of all other known causes of right ventricular strain, especially chronic pulmonary disease, mitral stenosis and congenital heart disease. In the presence of clear lung fields and in the absence of murmurs the differential diagnosis is comparatively easy. Unfortunately, in many cases murmurs, and even thrills, develop during the course of the disease, and in some instances the lung fields become obscured, from pressure due to effusion in the pleural and the pericardial sacs, from infarctions, from edema of congestion or from low grade inflammatory processes.

Several authors have stressed the importance of cyanosis in a degree out of proportion to the amount of dyspnea as a sign in favor of primary

pulmonary vascular sclerosis. In cor pulmonale secondary to pulmonary disease dyspnea is more apt to equal or exceed in degree the prevailing cyanosis.

ETIOLOGY AND PATHOGENESIS

Concerning the nature of the pathogenic process affecting the pulmonary vessels nothing definite is known. Probably many variable factors are involved, since great variation is encountered in the character and location of the lesions, as well as in their severity. In some instances the microscopic changes suggest a possible infectious process; in others the changes appear to be degenerative and are similar to those which commonly attack the systemic vessels. Yet notwithstanding this variability of the pulmonary vascular lesions, the anatomic changes of the right ventricle and the resultant clinical manifestations are remarkably uniform in all cases. This circumstance, together with the fact that extensive obstructive disease of the pulmonary vascular bed may occur without any apparent right ventricular strain and without any clinical symptoms, raises the question whether an etiologic relation between the pulmonary arterial disease and the strain of the right side of the heart may be regarded as definitely established.

However, although it may be admitted that such relation cannot be proved for all cases, it can be shown from both experimental and clinical observations that obstructive pulmonary vascular disease may produce severe and fatal strain of the right side of the heart, with the complete clinical picture which characterizes the special group of cases under discussion. Experimentally this syndrome has been repeatedly produced in dogs by graded compression of the pulmonary artery, with uniform results.²² Clinically, manifestations similar to those seen in severe types of primary pulmonary arteriolar sclerosis with identical anatomic changes in the right cardiac chambers have been observed to develop rapidly from obliteration of the pulmonary vascular bed by metastatic carcinoma.²³ The conclusion therefore appears justified that at least in some of the cases the obliterative pulmonary vascular disease bears a direct etiologic relation to the accompanying changes in the right side of the heart and the resultant clinical manifestations.

The uniform character in almost all cases of the anatomic alterations of the right cardiac chambers suggests that these alterations represent a response to a common factor, possibly pulmonary hypertension. The hypothesis naturally suggests itself that all these cases, whether or not there is associated pulmonary vascular disease, represent primarily a

22. Fineberg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, *Am. Heart J.* **11**:255-263 (March) 1936.

23. Greenspan, E. B.: Carcinomatous Endarteritis of the Pulmonary Vessels Resulting in Failure of the Right Ventricle, *Arch. Int. Med.* **54**:625-644 (Oct.) 1934. Brill and Robertson.³

physiopathologic response to pulmonary hypertension of unknown origin, perhaps analogous to essential systemic hypertension. The assumption of this hypothesis implies further that such changes in the pulmonary vessels as may be found are merely secondary to the hypertension, that these changes may or may not attain important proportions and that the resultant clinical picture, being dependent chiefly on the pulmonary hypertension, is not significantly affected by the degree of the associated pulmonary vascular damage. This theory receives possible confirmation from the fact that loud, booming pulmonic second sounds and violently pulsating pulmonary arteries as seen under the fluoroscope are observed with equal regularity in those cases in which no pulmonary arteriosclerosis is found, as well as in those in which extensive pulmonary vascular disease is present.

Unfortunately, no clinically satisfactory method for testing the blood pressure of the lesser circuit is as yet available, and until such a method is developed the attractive theory of essential pulmonary hypertension must remain an interesting but unproved speculation.

SUMMARY

A discussion of the literature on primary pulmonary arteriosclerosis is presented with the report of a case recognized during life.

The signs and symptoms are analyzed for a group of 20 cases selected from the literature and including the case now reported.

Principles of diagnosis are suggested.

Theories concerning etiology and pathogenesis are discussed, with especial reference to the possibility of an essential pulmonary hypertension bearing a relation to strain of the right side of the heart analogous to the effect of essential systemic hypertension on the left side of the heart.

RESPONSE OF NORMAL SUBJECTS TO ACUTE BLOOD LOSS

WITH SPECIAL REFERENCE TO THE MECHANISM OF
RESTORATION OF BLOOD VOLUME

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Studies on the response of the body to acute blood loss are of both theoretic and practical importance because hemorrhage is a serious complication in many medical and surgical conditions. In man, controlled observations on the effect of hemorrhage on the circulation, the plasma volume, the protein concentration and the cell-plasma ratio are difficult to obtain because the immediate care of the patient requires the complete attention of the physician and because the amount of blood lost is not known. In addition, the underlying disease producing the hemorrhage may alter the response of the body.

Although many investigators have studied the effect of acute blood loss on lower animals, few studies on human subjects have been made under controlled conditions. Keith¹ observed changes in hematocrit reading and blood volume as determined by the dye method after the removal of 800 cc. of blood from a normal man. He found that one hour after removal of the blood the plasma volume had risen above the value obtained before hemorrhage, although the hematocrit reading remained unchanged. Waterfield² determined the blood volume by the carbon monoxide method in 2 subjects after the removal of 550 cc. of blood. In 1 case the blood volume determined immediately after hemorrhage was 670 cc. above the prehemorrhage level, while in the other it was 210 cc. lower. .

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1. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Council, Special Report Series, no. 27, London, His Majesty's Stationery Office, 1919.

2. Waterfield, R. L.: The Effects of Posture on the Circulating Blood Volume, *J. Physiol.* **72**:110 (June 6) 1931.

Because of lack of evidence on the subject, the effect of acute blood loss on normal subjects under controlled conditions was studied.

METHOD

Six normal professional blood donors who had not given blood during the previous six months served as subjects for the experiments. They were hospitalized for the duration of the study. The morning after their admission the basal plasma volume was determined by the dye method of Gibson and Evans³ as adapted to the Evelyn microcolorimeter.⁴

The cell-plasma ratio was determined by the hematocrit, with a 1.6 per cent solution of potassium oxalate used to prevent coagulation.³ The total red cell volume was calculated from the plasma volume and the hematocrit reading. The concentration of hemoglobin was determined by the method of Evelyn⁵; the serum protein concentration, by the falling drop method as described by Kagan.⁶ The total circulating protein, in grams, was obtained by multiplying the serum protein concentration, in grams per hundred cubic centimeters, by the plasma volume, in hundreds of cubic centimeters. The samples of blood were taken without stasis. Twenty-four to forty-eight hours later venesection was performed with the subject in the basal state and in a horizontal position. The protein concentration, the hemoglobin concentration, the hematocrit reading and the plasma volume were followed for the next three to four days. In 3 subjects 1,000 cc. of physiologic solution of sodium chloride was given immediately after venesection. All subjects were given 10 to 15 mg. of paredrinol sulfate (α -N-dimethyl-p-hydroxyphenethylamine sulfate) intravenously on the day of venesection to determine whether this drug was effective in raising the arterial pressure in the presence of a diminished blood volume. These results will be reported later. With 1 exception, the plasma volume was not determined for at least four hours after administration of the drug (table). The subjects fasted twelve hours before venesection and continued to fast for twelve hours after venesection. Thereafter they were on the ordinary hospital diet. Water was not restricted at any time.

RESULTS

Changes in Blood Pressure, Pulse Rate and Clinical Condition.—In the 6 subjects studied 760 to 1,220 cc. of blood, or from 15.5 to 19.7 per cent of the blood volume, was removed in six to thirteen minutes. The entire procedure was painless; the subjects could not see the blood,

3. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Clinical Application of Method Employing Azo Dye, "Evans Blue," and Spectrophotometer, *J. Clin. Investigation* **16**:301 (May) 1937.

4. Gibson, J. G., II, and Evelyn, K. A.: Clinical Studies of Blood Volume: Adaptation of Method to Photoelectric Micro-Colorimeter, *J. Clin. Investigation* **17**:153 (March) 1938.

5. Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters, *J. Biol. Chem.* **115**:63 (Aug.) 1936.

6. Kagan, B. M.: A Simple Method for the Estimation of the Total Protein Content of Plasma and Serum: II. The Estimation of the Total Protein Content of Human Plasma and Serum by Use of the Falling Drop Method, *J. Clin. Investigation* **17**:373 (July) 1938.

Effect of Venesection on Six Normal Subjects

Date	Time	Hematocrit Reading, Percentage	Hemo- globin, Gm. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Plasma Volume, Cc.	Red Cell Volume, Cc.	Total Blood Volume, Cc.	Theoretic Red Cell Volume, Cc.	Total Circulating Protein, Gm.	Protein Added After Bleeding, Gm.	Procedure
J. O., male, age 33, ht. 176 cm., wt. 80 Kg.											
2/1/40.....	9:10 a.m.	48.2	2,980	2,770	5,750	203	..	1,070 cc. of blood removed (plasma 530 cc., cells 520 cc.)
2/2/40.....	9:33 a.m.	48.8	16.25	6.80	
	9:39-9:47	
	9:51	48.4	16.05	6.50							
	10:07	47.4	15.80	6.42							
	10:23	46.7	15.40	6.30	2,660	2,310	5,000	2,230	167	4	
	10:27	15 mg. paredrinol sulfate i.v.
	11:51	47.1	15.10	6.30						..	
	4:35 p.m.	44.8	14.80	6.40	2,900	2,260	5,260	2,160	186	23	
2/ 3/40.....	9:30 a.m.	42.3	13.20	6.32							
2/ 4/40.....	9:30 a.m.	41.0	12.90								
2/ 5/40.....	9:15 a.m.	38.6	12.20	6.20	3,360	2,120	5,480	2,130	208	53	
R. C., male, age 35, ht. 174 cm., wt. 61.4 Kg.											
2/ 8/40.....	9:45 a.m.	46.9	14.6	7.00	2,590	2,280	4,870	181	
2/ 9/40.....	9:26 a.m.	47.5	15.4	7.10	760 cc. of blood removed (plasma 335 cc., cells 365 cc.)
	9:31-9:39	
	9:37	40.7	15.3	7.00							
	9:48	45.0	14.9								
	10:07	44.9	14.6	6.60							
	10:27	44.3	14.8	6.51	2,310	1,860	4,200	1,900	152	1	
	10:35	10 mg. paredrinol sulfate i.v.
	11:52	44.2	14.9	6.90							
	1:50 p.m.	42.2	13.9	6.80							
	5:20 p.m.	41.3	13.7	6.60	2,530	1,790	4,320	1,860	167	20	
2/10/40.....											
2/11/40.....	9:45 a.m.	38.2	13.1	6.62							
2/12/40.....	11:00 a.m.	37.4	6.62							
	9:10 a.m.	35.5	11.6	6.44	3,200	1,760	4,960	1,820	203	61	
M. K., male, age 21, ht. 163 cm., wt. 63.2 Kg.											
2/27/40.....	9:30 a.m.	43.9	6.90	2,810	2,230	5,070	196	..	1,000 cc. of blood removed (plasma 510 cc., cells 460 cc.)
2/28/40.....	9:23 a.m.	44.5	14.9	7.00	
	9:32-9:40	

[illegible]

Effect of Venesection on Six Normal Subjects—Continued

Date	Time	Hematocrit Reading, Percentage	Hemo-globin, Gm. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Plasma Volume, Cc.	Red Cell Volume, Cc.	Total Blood Volume, Cc.	Theoretic Red Cell Volume, Cc.	Total Clotting Protein, Gm.	Protein Added After Bleeding, Gm.	Procedure
T. W.—Continued											
	11:45	39.4	6.07							
	12:30 p.m.	39.4	13.7	6.32							
	1:20	41.3	13.9							
	2:30	41.1	14.0	6.60							
	4:40	40.5	14.0	6.62	3,210	2,210	5,420	2,370	213	5	
	9:00	40.1	13.7	6.62	3,545	2,165	5,710	2,350	223	21	
4/16/40.....	10:02 a.m.	37.9	12.5	6.44							
	4:30 p.m.	35.4									
4/17/40.....	9:43 a.m.	34.2	11.5	6.23	3,910	2,060	6,000	2,320	215	11	
4/18/40.....	11:15 a.m.	35.2	11.7	6.62							
4/19/40.....	9:21 a.m.	33.2	11.4	6.50	4,130	2,050	6,180	2,300	203	70	
A. B., male, age 38, ht. 160 cm., wt. 58.6 Kg.											
4/ 1/40.....	11:00 a.m.	47.0	2,350	2,280	4,630	173	..	800 cc. of blood removed (plasma 410 cc., cells 390 cc.)
4/ 3/40.....	9:50 a.m.	47.0	14.9	6.70	
	9:59-10:07	10 mg. paredrinol sulfate i.v.
	10:11	
	10:27	45.0	14.6	6.42							
	10:31	1,000 cc. physiologic solution of sodium chloride i.v. started
	10:47	41.4	13.2	5.90							
	10:59	39.4	12.7	5.60							
	11:10	Injection of saline solution completed
	11:12	37.6	12.3	5.50							
	11:37	39.2	12.7	5.70							
	12:22 p.m.	40.3	13.3	5.90							
	12:49	39.2	13.4	5.84							
	2:05	38.0	12.5	5.84							
	3:37	37.4	12.0	5.70	2,800	1,730	4,620	1,810	104	21	
4/ 4/40.....	9:15 a.m.	38.5	12.7	6.00							
4/ 5/40.....	9:15 a.m.	35.8	11.7	6.30							
4/ 6/40.....	9:15 a.m.	34.2	10.9	6.20	3,130	1,620	4,750	1,810	104	51	

and their attention during venesection was distracted by conversation. Circulatory collapse developed in 5 subjects; the sixth had no symptoms.

None of the subjects complained of any symptoms until near the end of venesection, though moderate pallor, cool hands and slight sweating of the forehead appeared. The onset of collapse was sudden, occurring in 2 subjects while the blood was being taken and in 3 subjects from one to four minutes after venesection was completed. In 4 subjects the arterial pressure and the heart rate were carefully followed. Before the onset of collapse there was only a slight fall in the systolic pressure (average 11 mm. of mercury), while the diastolic pressure remained unchanged; the heart rate increased 14 to 30 beats above the basal level. With the onset of collapse both the systolic and the diastolic pressure fell precipitously, and the heart rate became strikingly slow, ranging between 36 and 40 beats per minute. The subjects complained of weakness, nausea, a sensation of weight on the epigastrium and blurred vision. An ashen gray pallor developed, and they retched, perspired profusely and responded slowly, if at all, to commands. One subject became unconscious.

The subjects were placed in the Trendelenburg position when collapse developed. In the 2 subjects with collapse who received no medication, the heart rate remained slow and the systolic pressure below 100 mm. of mercury for thirty minutes. During the next twelve hours they were pale, but their circulation appeared adequate as long as they were recumbent. On standing up, however, they fainted. The other subjects were not allowed out of bed for twenty-four hours after venesection.

✧ *Changes in Plasma Volume Following Venesection.*—Immediately after hemorrhage there was a sharp drop in plasma volume (table; fig. 1). The plasma volume then gradually increased, until at the end of three to four days it was greater than the original plasma volume by an amount approximately equal to the volume of red blood cells removed. In the 3 cases in which physiologic solution of sodium chloride was not given intravenously determinations of plasma volume were performed thirty-six to one hundred and eleven minutes after hemorrhage. During this brief period the plasma volume increased only 145 to 230 cc., although in these 3 cases 760 to 1,070 cc. of blood had been removed. In none of them, therefore, was there a sudden large increase in plasma volume immediately following hemorrhage. Figure 1 shows the changes in plasma volume following hemorrhage over a period of three days in subject M. K.

✧ *Relation of Increase in Plasma Volume to Changes in Serum Protein Concentration.*—Immediately after the hemorrhage the total circulating protein was diminished by approximately the amount of protein

removed during venesection. In the first two hours after bleeding the increase in plasma volume was accompanied by a decrease in serum protein concentration and by only a slight increase in total circulating protein. In the 3 cases in which the plasma volume was determined within two hours after hemorrhage the average addition of protein to the plasma was only 5 Gm. This initial increase in plasma volume, therefore, was the result of the addition of a protein-poor fluid to the blood stream. In the 3 subjects who did not receive physiologic solution of sodium chloride this initial period of dilution was completed in less

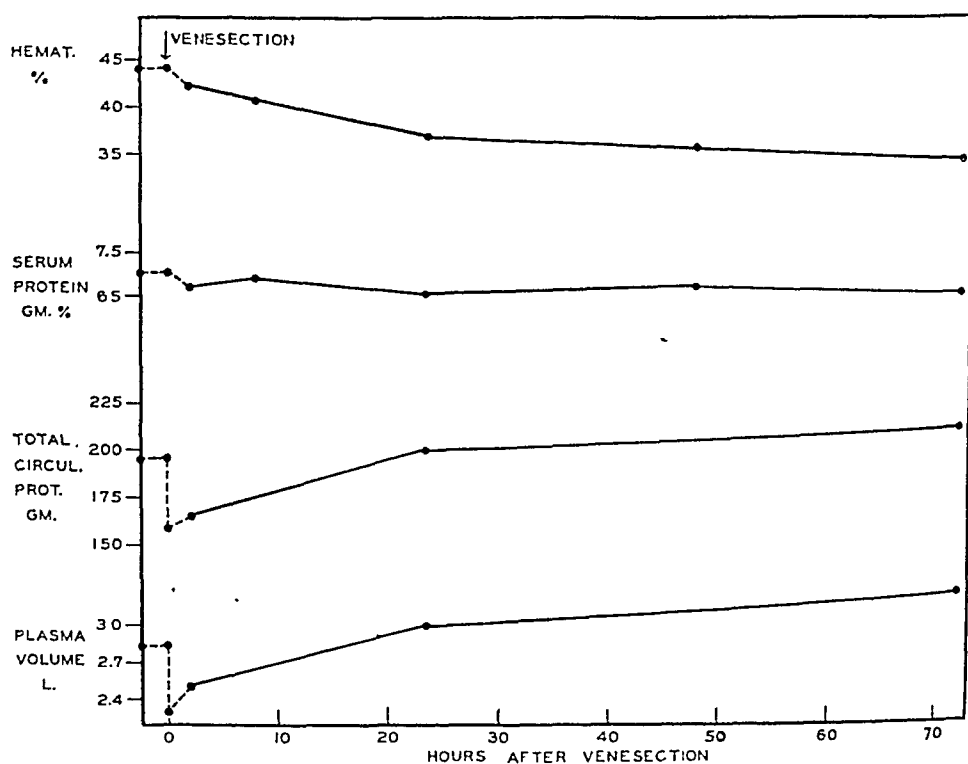


Fig. 1.—Effect of removal of 1,000 cc. of blood (540 cc. of plasma and 460 cc. of red cells) on plasma volume, hematocrit reading, serum protein concentration and total circulating protein in subject M. K.

than two hours. Thereafter, the concentration of the serum protein either did not change or increased slightly (fig. 1). This means that after the initial period of dilution the increase in plasma volume was accompanied by a simultaneous increase in total circulating protein. As protein and fluid were added to the blood at the same time, the protein concentration did not fall as the plasma volume increased.

In 3 cases 1,000 cc. of physiologic solution of sodium chloride was administered intravenously after venesection to determine whether the fluid would be retained in the blood stream. In 2 (J. F. and T. W.) the results were similar. During and after the administration of physio-

logic solution of sodium chloride there was a sharp drop in protein concentration, although never to the level one would expect if all of the solution had been retained within the vascular system. There was a corresponding drop in hematocrit readings (fig. 2). During the three hours after the saline solution was injected the serum protein concentration and the hematocrit reading rose, an indication that fluid was leaving the blood stream. After this period the serum protein concentration remained approximately constant while the hematocrit reading fell, showing that both fluid and protein were being added to the blood stream.

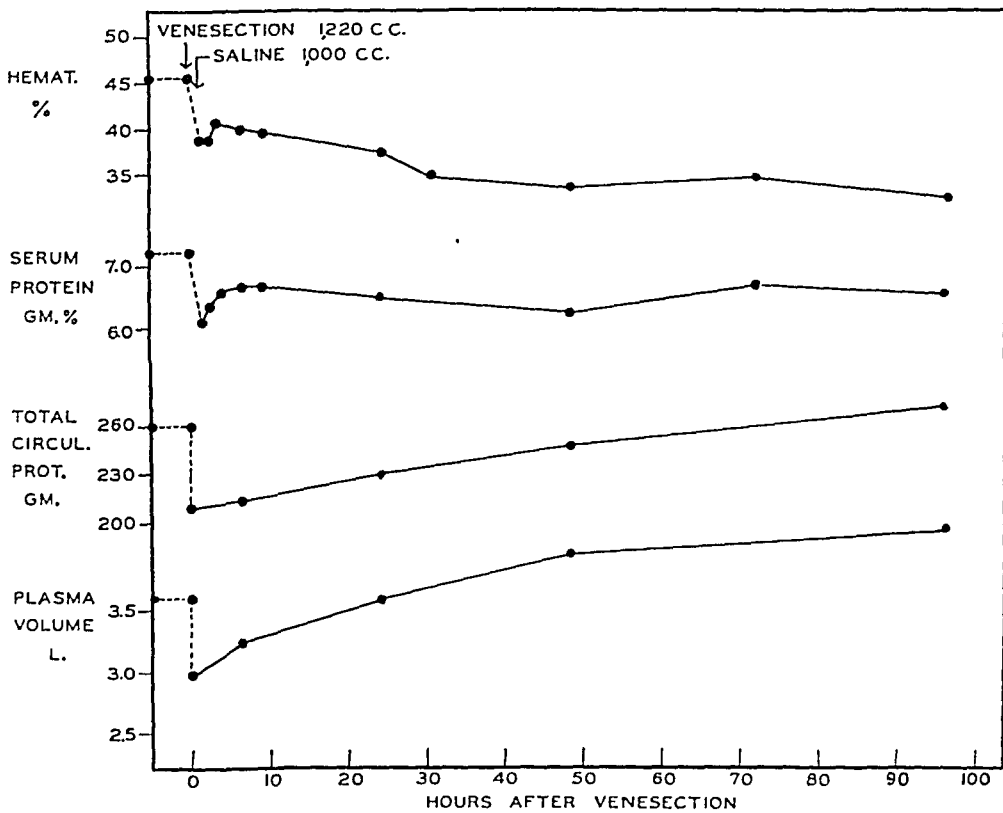


Fig. 2.—Effect of removal of 1,220 cc. of blood (620 cc. of plasma and 600 cc. of red cells) on plasma volume, hematocrit reading, serum protein concentration and total circulating protein in subject J. W. One thousand cubic centimeters of physiologic solution of sodium chloride was given intravenously thirty-three minutes after completion of venesection.

Values for plasma volume determined in these cases three and one-third and five hours, respectively, after administration of physiologic solution of sodium chloride were still 270 and 370 cc., respectively, lower than the prehemorrhage level. In the third case (A. B.) in which such a solution was administered, the dilution lasted much longer. Five hours after hemorrhage the plasma volume was higher than the original prehemorrhage value, and the lowered serum protein concentration showed that considerable dilution was still present.

^ A study of the qualitative changes in the various plasma proteins was made by Luetscher, using the electrophoretic method.⁷ In 3 cases he found no difference in the relative proportion of the albumin and the various globulin fractions in samples of blood taken before hemorrhage and in those taken three days after hemorrhage.

— *Changes in the Hematocrit Reading.*—In those cases in which physiologic solution of sodium chloride was not administered the hematocrit reading gradually fell after hemorrhage. The decrease in hematocrit value paralleled the increase in plasma volume and proved a useful guide in estimating the rate at which the plasma volume was increasing. If the difference between the original hematocrit reading and that made seventy-two hours after venesection is taken as 100 per cent, it is found that 14 to 36 per cent of this drop occurred in two hours, 36 to 50 per cent in eight hours and 63 to 77 per cent in twenty-four hours. Figure 1 shows the decline in hematocrit values in 1 case.

In those cases in which physiologic solution of sodium chloride was given after the bleeding, there was always an immediate drop in hematocrit values due to dilution of blood by the saline solution. This was followed by an increase in values as the solution left the blood stream (fig. 2).

Changes in Red Cell Volume.—At varying periods after hemorrhage the red cell volume was estimated from the plasma volume and the hematocrit reading. This was compared with the predicted red cell volume, which was calculated by subtracting from the red cell volume as determined before bleeding the volume of red cells removed by venesection and by sampling. The results are shown in the table. In the 3 cases in which the blood volume was measured within two hours after hemorrhage, before there was much change in the hematocrit value, the predicted and the determined red cell volume agreed closely (average difference, 1.9 per cent). After dilution had occurred and the hematocrit level had fallen, the predicted and the determined red cell volume no longer agreed. The determined red cell volume was lower than the predicted red cell volume in 5 subjects. In the sixth they were the same. The difference in any 1 case was too small to be significant in itself, but since the discrepancies were always in the same direction, that trend was believed to be significant. Likewise, the red cell volume determined shortly after hemorrhage was always 5 to 12 per cent higher than the red cell volume determined three days later, although only a small amount of blood for samples had been removed in the interim. Similar results have been obtained in bleeding experiments on

7. Luetscher, J. A., Jr.: Electrophoretic Analysis of Plasma and Urinary Proteins, *J. Clin. Investigation* **19**:313 (March) 1940.

splenectomized dogs.⁸ It appears that the total red cell volume cannot be accurately calculated from the plasma volume and the hematocrit reading because, as suggested by Smith, Arnold and Whipple,⁹ the cell plasma ratio in large and in small blood vessels is different. This problem will be discussed in detail in a later paper.

COMMENT

These experiments show that if 15 to 20 per cent of the normal blood volume (as determined by the dye method³) is rapidly removed from the body circulatory collapse will usually occur. It has been demonstrated previously that an average of 15 per cent of the blood circulating in the head and trunk can be pooled in the extremities by venous tourniquets and that this pooling will produce collapse in some normal subjects.¹⁰ In the experiments with venesection and with tourniquets the blood was removed rapidly. Probably more blood could be removed without producing symptoms if it was done slowly. In spite of the precautions taken, psychic and reflex factors undoubtedly played some part in the onset of the collapse. It is possible that if the experiments had been repeated several times on the same subject more blood could have been removed before collapse occurred.

The onset of the collapse was sudden. Until it occurred the subject had no complaints. In 3 subjects, collapse developed from one to four minutes after venesection was completed. The compensatory mechanism appeared to break down suddenly, even though no more blood was being removed and the position of the subject had not been changed. Before the onset of collapse the heart rate increased moderately, presumably because of the effect of the fall in systolic pressure on the carotid sinus and on other pressor reflexes. At the height of collapse the heart rate became extremely slow. A similar slow heart rate has been noted in certain types of clinical shock, in vasovagal syncope and in advanced stages of collapse induced by sodium nitrite. As pointed out by Weiss, Wilkins and Haynes,¹¹ subjects at the height of collapse induced by

8. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, *Am. J. Physiol.* **132**:411 (March) 1941.

9. Smith, H. P.; Arnold, H. R., and Whipple, G. H.: Blood Volume Studies: VII. Comparative Values of Welcker, Carbon Monoxide and Dye Methods for Blood Volume Determinations; Accurate Estimation of Absolute Blood Volume, *Am. J. Physiol.* **56**:336 (June) 1921.

10. Ebert, R. V., and Stead, E. A., Jr.: The Effect of the Application of Tourniquets on the Hemodynamics of the Circulation, *J. Clin. Investigation* **19**:561 (July) 1940.

11. Weiss, S.; Wilkins, R. W., and Haynes, F. W.: The Nature of Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **16**:73 (Jan.) 1937.

sodium nitrite show signs of overactivity of both the sympathetic and the parasympathetic nervous system. It is not known whether ischemia stimulates the parasympathetic centers in the central nervous system directly or reflexly.

The decrease in blood volume by hemorrhage is apparently compensated in two ways: (1) by vasoconstriction and (2) by addition of fluid to the blood stream. The vasoconstriction is shown by pallor, cooling of the extremities and narrowing of the pulse pressure. The addition of fluid to the blood stream is demonstrated by the gradual increase in blood volume. This is accounted for entirely by the increased plasma volume, and there are no demonstrable reserves of red cells which are added to the blood stream in this type of emergency. In the first two hours after venesection the plasma volume is increased by fluid poor in protein. This causes the serum protein concentration to fall. Thereafter, fluid and protein are added to the blood stream at the same time, so that, though the plasma volume continues to increase, the protein concentration falls no farther.

This initial fall in the plasma protein concentration immediately after severe hemorrhage is a well recognized phenomenon. It has been suggested that fluid is added to the blood stream immediately after hemorrhage because of the decreased capillary pressure, which allows the osmotic pressure of the proteins to draw water into the blood stream.¹² The slow increase in plasma volume is not the result of the lack of fluid in the body with which to dilute the blood, because when physiologic solution of sodium chloride is given intravenously the dilution is not maintained. In these experiments it appears that after the initial period of dilution the size of the plasma volume is determined by the quantity of circulating protein. Therefore, a large increase in plasma volume is not maintained until the amount of circulating protein has been increased.

It is established that in cases of surgical shock and of profuse hemorrhage with marked fall in blood pressure physiologic solution of sodium chloride is ineffective in treatment and that only the administration of whole blood or of plasma will produce a lasting rise in blood pressure. Apparently the diminished blood volume can be increased to only a limited degree of the addition of protein-free fluid. Beyond this point it is necessary to add a substance which increases the colloid osmotic pressure of the blood in order to increase the blood volume further. In patients with low plasma protein due to the nephrotic syndrome¹³ or to

12. Adolph, E. F.; Gerbasi, M. J., and Lepore, J. J.: The Rate of Entrance of Fluid into Blood in Hemorrhage, *Am. J. Physiol.* **104**:502 (May) 1933.

13. Harris, A. W., and Gibson, J. G., II: Clinical Studies of the Blood Volume: VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, *J. Clin. Investigation* **18**:527 (Sept.) 1939.

nutritional deficiency¹⁴ the blood volume is low, and with an increase in plasma protein there is an increase in blood volume. In these chronic conditions the amount of total circulating protein is one of the most important factors regulating the blood volume.

Large amounts of protein are not added to the blood stream immediately after hemorrhage, but there is a steady addition of protein for two to three days after venesection. About one fourth of the protein present seventy-two hours after hemorrhage was protein which had entered the blood stream since venesection. The proportions of the albumin and various globulins composing the plasma protein had not changed, indicating that the decrease in blood volume and serum protein caused by hemorrhage had served as a physiologic stimulus for the formation of normal serum protein. The fact that only small amounts of protein were added during the first two hours after venesection shows that the protein is not stored in plasma depots which can be readily emptied into the general circulation, but either that it is stored as prepared protein outside the circulation or that the materials to make the protein are readily available.

Extensive studies on the rate of regeneration of plasma proteins after plasmapheresis have been made on dogs.¹⁵ Immediately after removal of the protein there is no sudden large addition of protein to the blood stream, but a slow, steady regeneration over a period of days, which occurs even if the dog is fasting or is on a protein-poor diet, although it is more rapid on a meat diet. It has been found that if dogs are kept on a protein-deficient diet and subjected repeatedly to plasmapheresis, the plasma proteins are produced more rapidly during the first two to four weeks than later. The excess protein regenerated during this period has been called the protein reserve, and is probably composed chiefly of materials necessary to make the plasma proteins rather than of complete plasma proteins which can enter the blood stream immediately.

The hematocrit readings accurately reflected the direction of the changes in plasma volume in these experiments. An increase in plasma volume caused the reading to fall, and a decrease caused it to rise. After the first two hours the change in plasma volume was much more accurately reflected by the hematocrit value than by the protein concen-

14. Chang, H. C.: Plasma Protein and Blood Volume, *Proc. Soc. Exper. Biol. & Med.* **29**:829 (April) 1932.

15. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Proteins: I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion, *Am. J. Physiol.* **47**:356 (Dec.) 1918. Smith, H. P.; Belt, A. E., and Whipple, G. H.: Rapid Blood Plasma Protein Depletion and Curve of Regeneration, *ibid.* **52**:54 (May) 1920. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production, and Utilization, *Physiol. Rev.* **20**:194 (April) 1940.

tration. The continued increase in plasma volume was not shown by decreased protein concentration because protein was constantly being added to the blood stream, but it was shown by a steady fall in the hematocrit reading because no demonstrable number of red cells were added to the blood stream during the first three days after hemorrhage.

SUMMARY AND CONCLUSIONS

1. Seven hundred and sixty to 1,220 cc. of blood (15.5 to 19.7 per cent of the total blood volume as determined by the plasma volume and the hematocrit reading) was removed from 6 normal subjects in six to thirteen minutes. In 5 of the 6 subjects there developed collapse characterized by weakness, nausea, blurred vision, pallor, sweating and fall in arterial pressure. Before the onset of collapse the heart rate increased from 14 to 30 beats per minute. At the height of collapse the heart rate became slow, ranging between 36 to 40 beats per minute.

2. The plasma volume began to increase immediately after hemorrhage and continued to increase for the next forty-eight to seventy-two hours. At the end of seventy-two hours it was approximately equal to the plasma volume before hemorrhage plus the volume of red cells removed.

3. During the first two hours after venesection the plasma volume was increased by protein-poor fluid, so that the serum protein concentration decreased. Thereafter, fluid and protein were added to the plasma at the same time, and the serum protein concentration remained unchanged, though the total circulating protein increased.

4. At the end of seventy-two hours approximately one fourth of the plasma protein was protein which had been added to the plasma after venesection. Loss of blood acted as a physiologic stimulus for the production of normal protein, and the addition of the new protein did not change the proportions of the albumin and the various globulin fractions.

5. When physiologic solution of sodium chloride was given intravenously immediately after hemorrhage, it was not retained in the blood stream in sufficient quantity to restore the plasma volume to normal.

6. After hemorrhage the blood volume was not restored to normal until new plasma protein had been added to the circulation.

7. Hematocrit readings in these experiments accurately reflected the direction of a change in plasma volume.

CLINICAL LIPOID NEPHROSIS

WITH SPECIAL REFERENCE TO ITS TRANSFORMATION INTO CLINICAL
AND PATHOLOGIC CHRONIC GLOMERULONEPHRITIS

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DURHAM, N. C.

The purpose of this paper is to present a case of clinical lipid nephrosis which was studied over a period of four years and finally at autopsy. Nephritis with associated uremia developed terminally, and autopsy revealed the anatomic changes characteristic of chronic glomerulonephritis.

A brief statement regarding the controversies relating to the nature of lipid nephrosis may be presented to clarify the issues involved in this case.

One group of workers¹ has expressed the belief that lipid nephrosis is a separate clinical and pathologic entity distinct from chronic glomerulonephritis. Many of this group contended that patients with "pure" lipid nephrosis will either recover from this disease or die of an intercurrent infection. They also have stated that the diagnosis of lipid nephrosis is excluded even by the infrequent finding of a few red cells in the urine, slight elevations of blood pressure or a slight rise in blood nonprotein nitrogen. The other group² has expressed the opinion that lipid nephrosis represents simply a stage in the development of that pathologic process which ends in clinical and anatomic chronic glomerulonephritis. Findings in the case reported here constitute good evidence in support of the main thesis of the second group.

From the Department of Pathology, Duke University School of Medicine.

1. Murphy, F. D.; Warfield, L. M.; Grill, J., and Annis, F. R.: Lipoid Nephrosis, *Arch. Int. Med.* **62**:355 (Sept.) 1938. Aldrich, C. A.: Lipoid Nephrosis, in Brennemann, J.: *Practice of Pediatrics*, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 28, p. 21. Bell, E. T.: Lipoid Nephrosis, *Am. J. Path.* **5**:587 (Nov.) 1929. Fahr, G.: Lipoid Nephrosis, *Am. J. M. Sc.* **194**:449 (Oct.) 1937.

2. Blackman, S.: On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, *Bull. Johns Hopkins Hosp.* **57**:70 (Aug.) 1935. Bennett, T. I.; Dodds, E. C., and Robertson, J. D.: The Conception of "Nephrosis," *Quart. J. Med.* **24**:239 (Jan.) 1931. Christian, H. A.: Nephrosis: A Critique, *J. A. M. A.* **93**:23 (July 6) 1929. Mason, E. H.: The Life History of a Case of Nephrosis, *Internat. Clin.* **1**:163 (March) 1926.

REPORT OF A CASE

Clinical Summary.—(This summary was furnished by Dr. R. Charman Carroll, of the Duke Hospital department of pediatrics.) A 5 year old white girl was admitted to Duke Hospital three and one-half years before death, with the complaint of edema of the abdomen and legs. With rest in bed this condition had

Laboratory Data

Admission	Weight, Kg.	Blood Pressure, Mm. of Hg.	Urine, Specific Gravity	Blood Chemistry			Cholesterol, Mg./100 Cc.	Treatment *
				Non-protein Nitrogen, Mg./100 Cc.	Total Protein, Mg./100 Cc.	Albumin/Globulin		
1†	24.6	138/100	1.032	32	4.20	1/8	397	Acacia (3)
	15.9	1.030	30	5.00	4/5	395	Plasma (2)
2†	19.6	94/ 60	q.n.s.	25	3.60	Serum (2)
	16.1	q.n.s.	16	4.20	2/5	...	Whole blood (4)
3†	20.7	1.008	25	4.10	1/2	...	Magnesium sulfate (4)
	20.4	1.030	Theobromine with sodium salicylate (2)
4	20.6	120/ 74	27	4.30	3/5	...	Thyroid (5)
5	20.3	120/ 75	1.025	23	Ammonium chloride (3)
	20.0	Ammonium nitrate (1)
6	24.7	108/ 78	1.030	28	3.71	3.20	...	Potassium nitrate (1)
	21.8	1.025	..	2.61	1/5	182	Dextrose (3)
7	24.8	100/ 74	1.018	17	2.70	1/5	...	Sucrose (1)
	22.4	1.030	Urea (3)
8	22.7	102/ 78	1.026	38	2.80	1/4	...	Pitressin (1)
	22.6	Liver extract (1)
9	24.7	120/ 90	1.022	15	3.00	1/4	880	Quinine hydrochloride (1)
	21.7	1.020	26	Amino acids (1)
10	24.4	1.025	39	1,005	Paracentesis (7)
	20.9	1.030	33	3.64	...	960	Sulfanilamide (1)
11	25.5	120/ 80	1.020	58	3.70	...	1,140	Sulfanilamide (2)
	20.2	1.015	51	872	
12††	20.2	1.025	56	4.10	1/5	...	
	18.8	1.017	33	
13	25.8	155/130	1.014	342	356	

* A number in brackets indicates the number of times a type of therapy was given.

† Occasional red blood cells were found in the urine.

‡ The content of albumin in three twenty-four hour samples of urine was 3.4, 6.0 and 8.0 Gm., respectively, per hundred cubic centimeters.

cleared, but had returned and progressed to generalization when the patient again became ambulatory. No hematuria had been noted.

On the patient's first admission to the hospital, six months after appearance of the initial symptoms, the temperature was 38.5 C. (101.3 F.), the pulse rate 135, the respiratory rate 28 and the blood pressure 138 systolic and 100 diastolic. The child appeared acutely ill with extensive generalized pitting edema, ascites and pulmonary congestion. The tonsils were enlarged and infected. The hemoglobin concentration was 85 per cent, the red cell count 4,500,000 and the white cell count 16,700. The urine gave a 4 plus reaction for albumin, contained many white blood

cells and occasional red blood cells and hyaline casts and had a specific gravity of 1.032. The Wassermann reaction of the blood was negative (see table for other laboratory data).

During the next four months, the patient did not improve in spite of numerous types of therapy (see table), which included administration of 86 Gm. of acacia in doses of 15 to 23 Gm. Orbital abscesses and estivoautumnal malaria occurred during this period. In the fourth month of hospitalization, the urinary output increased rapidly and the edema receded without relation to specific therapy.

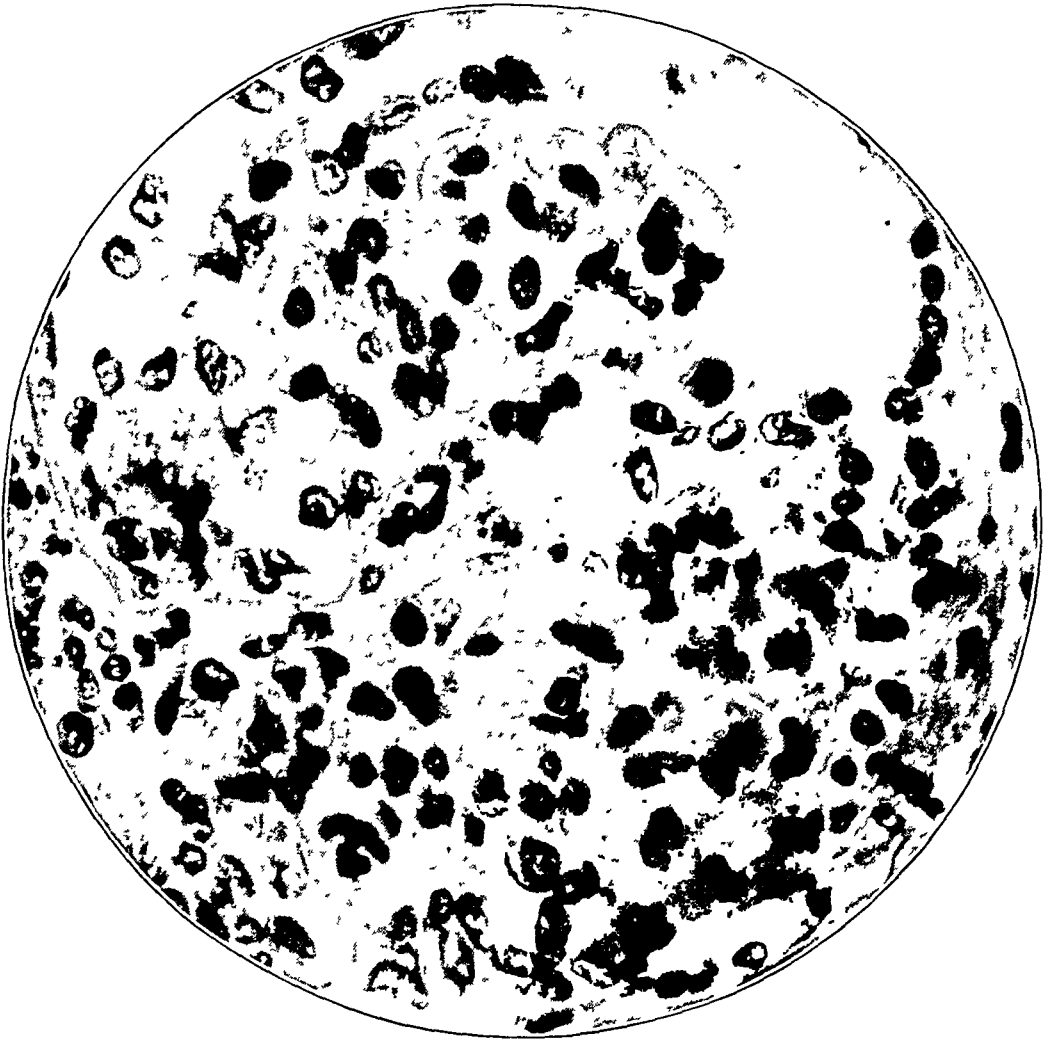


Fig. 1.—A typical glomerulus with widespread acute and chronic inflammatory reaction.

Throughout the period of observation urinalysis gave a 3 to 4 plus reaction for albumin, showed 0 to 8 red blood cells per high power field and few to many white blood cells and casts and had a specific gravity of 1.029 to 1.032.

Within the three years preceding death the child was admitted to the hospital twelve more times. One admission was for a tonsillectomy and adenoidectomy. The others, like the first, were for nephrotic attacks, lasting from two weeks to five months, and were usually associated with infections of the upper respiratory tract. Laboratory findings were similar to those of the first period of hospitalization, except that red blood cells were found in the urine in the course of only two

of the twelve periods (see table). Results of the phenosulfonphthalein excretion test and the basal metabolic rate were within normal limits.

The thirteenth and last admission occurred approximately four years after the initial attack of the child's long illness. At this time the complaint was generalized edema of one week's duration, cough, vomiting and fever of twenty-four hours' duration. The temperature was 37.9 C. (100.2 F.), pulse rate 120, respiratory rate 24 and blood pressure 155 systolic and 130 diastolic. The patient was acutely ill, lethargic and dyspneic. The complexion was waxy, and there was marked gen-

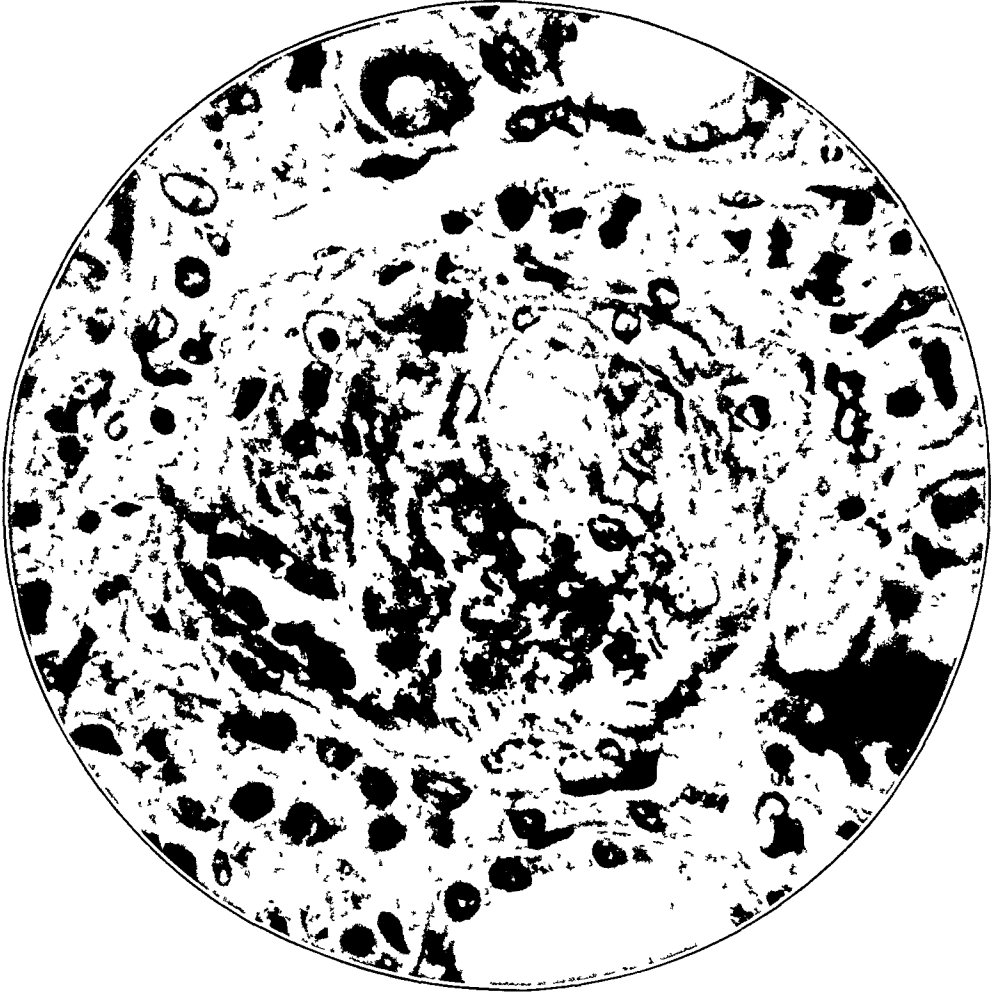


Fig. 2.—A completely hyalinized glomerulus.

eralized pitting edema with ascites and pulmonary congestion. The heart was enlarged in all diameters; the rate was rapid, but no murmurs were heard. The electrocardiogram indicated myocardial injury. The hemoglobin concentration was 45 per cent, the red cell count 2,770,000, and the white cell count 12,040. The carbon dioxide-combining power was 32 volumes per cent and the nonprotein nitrogen content 342 mg. per hundred cubic centimeters. Therapy consisted of administration of a molar solution of sodium lactate by mouth, small blood transfusions, intravenous injection of a 25 per cent solution of sucrose and paracenteses (cultures of the fluid were negative). The day following admission a friction rub was heard over the entire precordium. Edema increased, and the urinary output remained below 300 cc. per day. The child died suddenly one week after admission.

Clinically, this patient was thought to have nephrosis the diagnosis having been based on the following essential findings: continuous albuminuria with red blood cells observed infrequently (during only three of the thirteen periods of hospitalization); insidious onset of the illness without previous history of infection; normal level of nonprotein nitrogen until the last admission; pronounced edema, which recurred ten times; normal blood pressure, except on the first and last admissions; increased blood cholesterol, and low total serum proteins, with a reversal of the albumin/globulin ratio. However, terminally the clinical picture was no longer

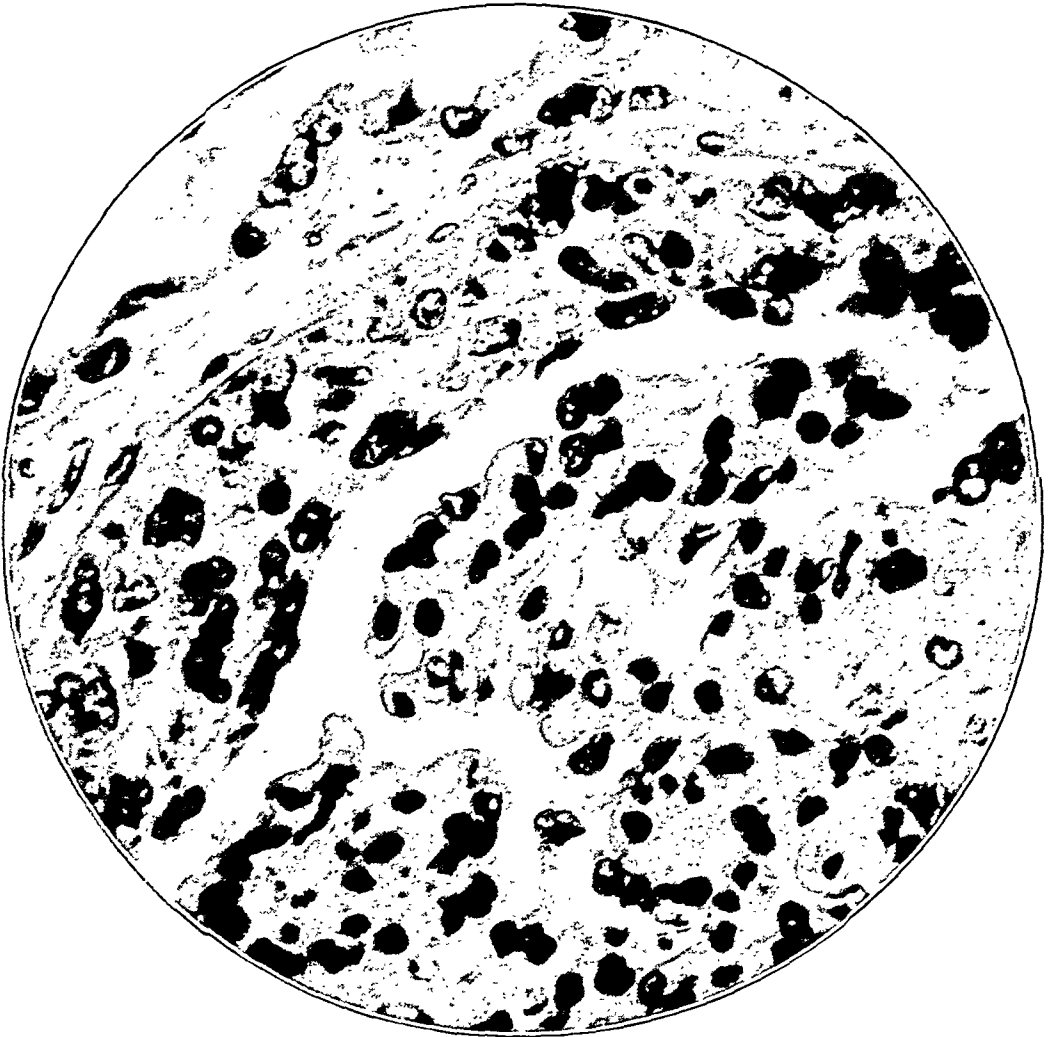


Fig. 3.—A glomerulus with a typical crescent.

that of nephrosis but that of typical glomerulonephritis with associated uremia (see table for data).

Autopsy Protocol.—The diagnoses made at autopsy included: chronic glomerulonephritis; cardiac dilatation; anasarca; fibrinous pericarditis (uremic); prominent fat deposits in the aortic and the mitral valves and in the intima of the coronary arteries and the aorta; submucosal edema of the colon and the bladder and storage of acacia in the liver.

Extreme anasarca was present. The abdominal cavity contained 880 cc. of a frothy cloudy fluid in which there were no bacteria. The heart weighed 100 Gm., which was within normal limits for a child of this age (8½ years) and height

(115 cm.). The cavities were considerably dilated. Fibrinous pericarditis was present. There were extremely fatty atheromatous plaques in the aortic and the mitral valves, in the coronary arteries and throughout the entire length of the aorta, where they were concentrated in the distal portion, there giving rise to considerable narrowing of the lumen. Microscopically these plaques appeared similar to those seen in the aortas of adults. Under the polarizing microscope, both in a section stained for fat (with scarlet red) and in an unstained frozen section, doubly refractile crystals of cholesterol esters were observed. Some of the stained fat

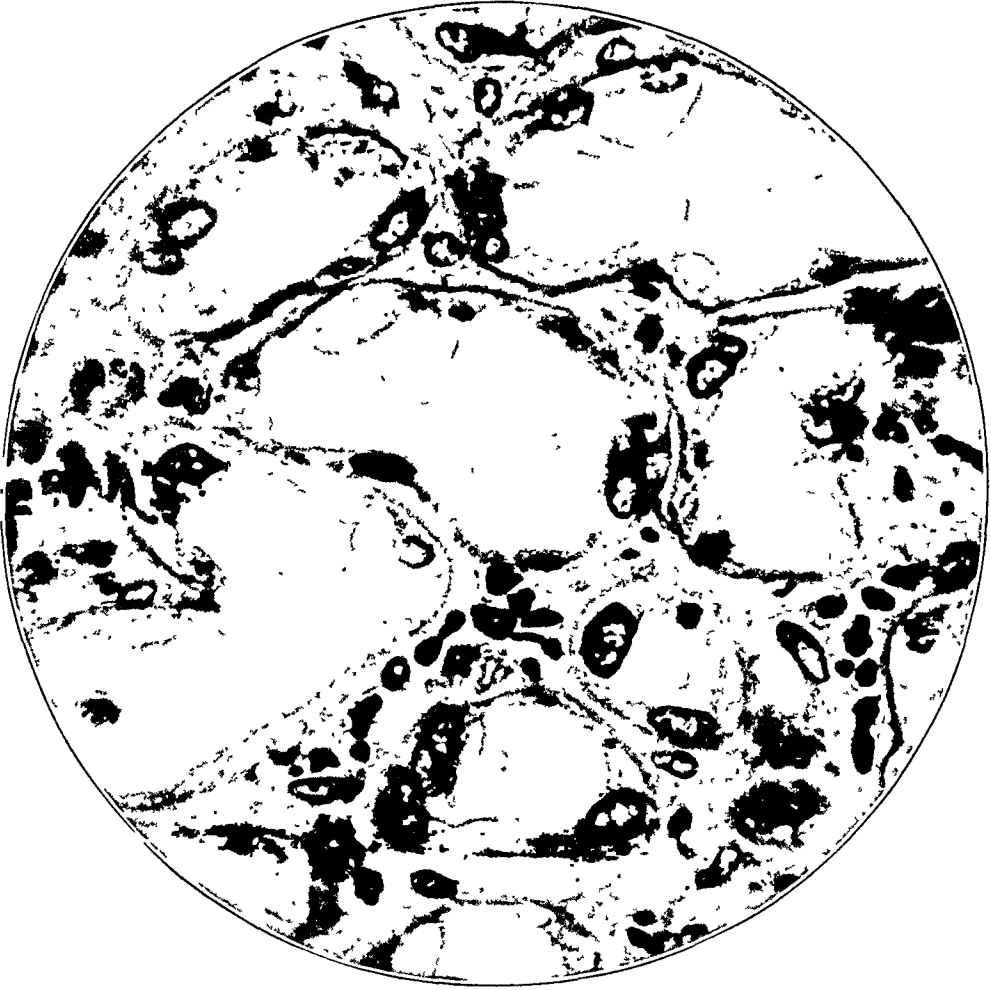


Fig. 4.—Dilated convoluted tubules containing coagulated protein and lined with small flat cells and large regenerating cells.

was not doubly refractile, and therefore it was recognized as neutral fat. The use of Nile blue sulfate stain confirmed this differentiation. Both lungs contained numerous small areas of atelectasis. The liver was large, weighing 1,070 Gm. The cut surface was swollen and puffy, with conspicuous lobules. Microscopically it appeared to contain acacia. This was confirmed by comparison with livers known to contain acacia and by chemical analysis. This aspect of the case, storage of acacia in the liver, is being reported separately. The submucosa of both the colon and the urinary bladder was edematous.

The weight of each kidney, 100 gm., was within normal limits considering the age and height of the patient. There was no variation in general appearance between

the two kidneys. The surfaces were pitted by fine shallow scars and spotted with many small hemorrhagic flecks. The cortex was narrow and brownish gray. Most of the cortical striae were irregular and distorted. The glomeruli exhibited a homogeneous eosinophilic supporting structure due to fibrosis, fibrinous exudate and hyaline alteration of the greatly thickened basement membrane (figs. 1 and 2). Many of the dilated capsular spaces were filled with coagulated protein. Numerous typical crescents were present (fig. 3). Glomeruli showing capsular adhesions covered with epithelium were conspicuous. Some of the glomeruli were the seat of extreme fat deposits. Only a small portion of the fat was cholesterol or its esters, as determined by examination with the polarizing microscope. Most of the convoluted tubules were dilated and contained coagulated protein (fig. 4). Some contained cellular casts and, in some instances, red blood cells. The tubular epithelium was flattened, and the cells seemed to be decreased in number. Interspersed among the flattened cells were large oval cells with vesicular nuclei thought to represent regenerating tubular epithelium. Similar changes were noted in the collecting tubules. Fat was contained in only a few of the tubular cells, and it was not anisotropic. The arterioles showed no changes. The interstitial tissue was infiltrated with lymphocytes and fibroblasts. The pelves showed no change.

COMMENT

Anasarca, albumin in the urine, lowered serum proteins, reversal of the albumin/globulin ratio, high blood cholesterol, normal blood pressure, normal nonprotein nitrogen and infrequent occurrence to complete absence of red blood cells in the urine were all exhibited in this case. The changes mentioned represent the usual criteria for the diagnosis of lipoid nephrosis. However, many authors would not consider the condition in this case a "pure" example, because of the red cells noted in the urine and the slightly elevated blood pressure present at the time of the patient's first admission to the hospital. On the contrary, my associates and I are inclined to agree with Blackman,³ who has expressed the opinion that there may be examples of lipoid nephrosis which are "pure" but in which there are an occasional rise in blood pressure and a few red cells in the urine. If the patient had had glomerulonephritis for four years we should have expected to find small contracted kidneys. Furthermore, the fact that the glomeruli showed both old and fresh lesions suggested that the process had been in progress some time before the clinical evidence of nephritis developed. Thus, it is obvious that there is only indirect pathologic evidence that the patient once had lipoid nephrosis. Nevertheless, these pathologic anatomic observations, coupled with the long duration of the disease, the thorough and continuous clinical observation and the laboratory data, have led us to believe that we are dealing with a case of lipoid nephrosis which was terminated not by recovery or by fatal intercurrent infection, as this disease so often is, but by the progressive devel-

3. Blackman, S.: *Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis*, Bull. Johns Hopkins Hosp. 55:1 (July) 1934.

opment of its basic pathologic process to the point that its final state was identical clinically and anatomically with chronic glomerulonephritis.

SUMMARY

A case is presented in which were exhibited all of the typical features of lipid nephrosis. The patient, a white child, was followed for four years, during which time careful clinical studies were facilitated by her being admitted to the hospital thirteen times. On the final admission it was discovered that the clinical picture had changed to such an extent that the diagnosis of lipid nephrosis was no longer tenable, since all of the typical signs and symptoms of chronic glomerulonephritis had developed. The terminal clinical diagnosis of chronic glomerulonephritis was confirmed by autopsy, which revealed the typical anatomic lesions of chronic glomerulonephritis.

The observations recorded in this case appear to support the thesis that lipid nephrosis and chronic glomerulonephritis are not separate and distinct anatomic entities but merely represent different manifestations or phases of one and the same general pathologic process, the natural history of which is progression to termination in failure of renal function.

Progress in Internal Medicine

VASCULAR DISEASES

SEVENTH ANNUAL REVIEW

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REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. VAN DELLEN AND DR. SCUPHAM

The continued interest in vascular problems and their clinical importance is evidenced by the numerous articles appearing in the world literature. Some new data have been added, with particular reference to physiologic aspects. Contributions to the medical management of patients with peripheral vascular disease have been surprisingly few, whereas many have appeared on the surgical management. We again bring to the attention of the reader the fact that this review is not complete, as many deserving articles have undoubtedly been missed.

PHYSIOLOGY

Reviews.—An excellent review of circulatory physiology was compiled by Hall.¹ He covers the large bibliography briefly but adequately, stressing the current advances in the study of the peripheral circulation and including such related topics as shock and the circulation in special regions.

Blood Flow.—Burton and Taylor² continue their study of the periodic fluctuations of vessel tone. They examined the changes under

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1. Hall, V. E.: Peripheral Circulation, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1941, vol. 3, p. 343.

2. Burton, A. C., and Taylor, R. M.: A Study of the Adjustment of Peripheral Vascular Tone to the Requirements of the Regulation of Body Temperature, *J. Physiol.* **129**: 565 (June) 1940.

various conditions of heat loss, mainly to determine the manner in which the fluctuations were modified to maintain an appropriate value for the average blood flow. Changes in finger volume with each heart beat were used as an index of general vascular tone.

Two types of constriction were noted: that responding to external stimuli, or that of "psychic" origin, and that considered to be "spontaneous." These are distinguished by the simultaneous recording of the psychogalvanic reflex, indicating sweat gland activity and measuring vasoconstriction of the "psychic type." By this method, the authors demonstrated that the sympathetic nerves to the blood vessels in the palm are completely independent of those to the sweat glands.

The regularity of the rhythm of spontaneous vasoconstriction was measured by statistical methods previously reviewed. The interval between constrictions in the "comfortable" range of environmental temperature varies from thirty seconds to two minutes, with an average of fifty to sixty seconds. As the environmental temperature is raised the average interval increases. The fluctuations are the same whether the subject is immersed in a water bath or exposed to air, an indication that the intermittence of tone is not due to a corresponding intermittence of cutaneous temperature.

The average size of each pulsation in the finger, calculated for five minute periods during both experiments, was remarkably constant. The authors also determined the average size of each pulsation between periods of vasoconstriction with rising environmental temperature and demonstrated the remarkable efficiency of temperature regulation by modifying the rhythmic fluctuations. They conclude that the reflex adjustment of the blood flow in the peripheral vessels, in accordance with the requirements of temperature regulation, is a continuous process, consisting in a corresponding modification of vascular tone, intrinsically rhythmic in character.

Spontaneous changes in volume were studied by Abramson and Katzenstein.³ Using a standard plethysmograph, the authors were able to find these fluctuations only in the hand, since they are insignificant in the forearm, leg and foot. They occur most frequently in the young and less frequently in the old and are rather marked during sleep. They disappear at high and at low temperatures. As the authors were able to make them disappear by raising the venous pressure to 60 or 70 mm. of mercury, they conclude that the spontaneous variations in the hand are due to alterations in the caliber of the venous bed.

3. Abramson, D. I., and Katzenstein, K. H.: Spontaneous Volume Changes in the Extremities, *Am. Heart J.* **21**:91 (Feb.) 1941.

Stewart and Evans⁴ and Abramson and Fierst⁵ confirm the existing belief that blood flow is increased in hyperthyroidism. The former authors used an improved radiometer, while the latter ones used a venous occlusion plethysmograph. All report a decrease in blood flow following the administration of iodine or thyroidectomy. Stewart and Evans also show that in hyperthyroidism the peripheral resistance is low, almost in an inverse ratio to the basal metabolic rate.

The value of the photoelectric plethysmograph is again stressed by Hertzman and Dillon.⁶ Its usefulness in distinguishing "active" from "passive" components and in separating arterial from venous reactions in the skin is suggested. In another article⁷ the authors describe its clinical application and cite instances of its usefulness in studying vascular reactions in cases of Raynaud's disease or in evaluating the completeness of a sympathetic denervation.

Using the same apparatus on the tissue supplied by the radial and digital arteries, Hertzman and Dillon⁸ studied the possibility of a synergistic participation of the larger arteries in the reactions of the small arteries and arterioles. Responses to a deep breath, to holding a deep breath, to the cold pressor test, to loud noises and to various psychic stimuli were noted. The participation of the radial artery in the vasoconstriction of the digital arteries is irregular but consistent in instances of massive disturbance of the circulation. The degree of constriction of the digital arteries has little predictive value with respect to the occurrence of constriction in the radial artery. The data do, however, show some selection with respect to the intensity of the participation of the radial artery in the vasomotor responses of the small arteries and the arterioles it supplies.

Dillon and Hertzman⁹ report some interesting observations on the volume pulse in the finger pads of healthy subjects and contrast them with their findings in arteriosclerotic and hypertensive patients. The normal digital pulse is essentially of the same contour as the radial

4. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, *Am. Heart J.* **20**:715 (Dec.) 1940.

5. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow in the Extremities in Hyperthyroid Subjects, *Proc. Soc. Exper. Biol. & Med.* **46**:39 (Jan.) 1941.

6. Hertzman, A. B., and Dillon, J. B.: Distinction Between Arterial, Venous and Flow Components in Photoelectric Plethysmography in Man, *Am. J. Physiol.* **130**:177 (July) 1940.

7. Hertzman, A. B., and Dillon, J. B.: Application of Photoelectric Plethysmography in Peripheral Vascular Disease, *Am. Heart J.* **20**:750 (Dec.) 1940.

8. Hertzman, A. B., and Dillon, J. B.: Reactions of Large and Small Arteries in Man to Vasoconstrictor Stimuli, *Am. J. Physiol.* **130**:56 (July) 1940.

9. Dillon, J. B., and Hertzman, A. B.: The Form of the Volume Pulse in the Finger Pad in Health, Arteriosclerosis, and Hypertension, *Am. Heart J.* **21**:172 (Feb.) 1941.

disease. They assume that in this disease the anastomosis is eventually turned from an active contractile vessel into a permanently patent channel through which blood flows uncontrolled directly into the venules. Patients with normal circulation were used as controls. In resting persons with impaired circulation, the venous blood from the foot carried more oxygen, and frequently less carbon dioxide, than did the venous blood from the forearm. Under such circumstances the content of lactic acid was relatively high. In normal subjects the opposite was noted, although the results were none too consistent. The authors are of the opinion that these findings indicate a patent arteriovenous anastomosis permitting the "shunting" of blood from the arterial to the venous side. In some cases the oxygen saturation was increased after exercise, but in the majority the opposite effect was noted. The level of lactic acid, on the other hand, was consistently elevated. In many cases analysis of samples of blood taken one-half hour after exercise revealed an oxygen deficit and a high lactic acid level, indicating an inadequacy of the peripheral circulation comparable to that occurring in normal persons recovering from fatigue. Although these observations are not entirely new, it is well to appreciate the role played by the anastomoses in determining the amount of blood available to the capillary bed. Increased blood flow through an extremity in which the anastomoses are patent does not necessarily mean that the capillary circulation to the tissues is augmented.

Solutions designed to replace blood as a perfusion medium for the study of capillary circulation must contain, according to Zweifach,¹⁴ not only appropriate chemical constituents but a suspension of formed elements, such as particles of carbon or red cells. The action of particulate matter is beneficial in that it produces a maximum distribution of the perfusate through all the vessels of the capillary bed. In the absence of red cells or carbon, the flow is restricted to the arteriovenous capillaries. By the addition of suspended matter the flow is diverted into the true capillaries. Particulate matter, especially red cells, is effective because it plugs up leaks in the walls of the vessels. Stasis in abnormally leaky vessels is considered an additional factor acting to prevent further loss of fluid by clogging these vessels and eliminating them from the active circulation.

Continuing this type of investigation, Chambers and Zweifach¹⁵ report their observations on the permeability of capillaries in the tongue and mesentery of the frog. They believe that the kind of permeability

14. Zweifach, B. S.: The Distribution of Blood Perfusates in Capillary Circulation, *Am. J. Physiol.* **130**:512 (Sept.) 1940.

15. Chambers, R., and Zweifach, B. W.: Capillary Endothelial Cement in Relation to Permeability, *J. Cell. & Comp. Physiol.* **15**:255 (June 20) 1940.

displayed by a membrane of the endothelial type can be explained without taking into account the cellular components of the vessels, concluding that the filtration barrier is divided into two constituents: the intercellular cement and an adsorbed layer of protein. This cement is spread over the inner surface of the endothelial cells, as well as between them and is continually washed away by the blood and replaced by secretion of the endothelial cells. If the perfusion fluid is acid or lacks calcium, the cement softens and is removed more rapidly. These conditions, as well as mechanical injury, favor extrusion of formed elements and outward diffusion of the fluid of the perfusate. The cement becomes sticky, and red corpuscles adhere to the injured areas, thus plugging leaks and maintaining normal permeability. Protein from the blood is also deposited on the intercellular cement. The authors suggest that although the intercellular cement is the actual filter, the pores of the filter may be clogged by the protein. Hence, changes in the porosity of the capillary wall, to the extent of permitting the colloidal constituents of the blood to leak through, may be due to the impairment of adsorption of the serum proteins to the inner surface of the vessel.

In addition, Zweifach¹⁶ stresses the importance of the anatomic arrangement of capillaries in the production of edema. Since only a few of the capillaries convey an active flow of blood in resting tissue, it would seem to follow that the inactive capillaries do not participate in the withdrawal of tissue fluid. The author shows that such a condition does not exist, as the presence of a circulation in the arteriovenous capillaries alone initiates a suction force which acts on the static true capillaries and therefore sets into motion a mechanism for fluid exchange between the capillary blood stream and the tissue spaces. Conditions which upset the suction prevent adequate inward diffusion and result in an excess of fluid in the tissue spaces.

Engel¹⁷ observed the influence of the sympathetic nervous system on capillary permeability in cats, rabbits and dogs. Capillary permeability is determined by injecting fuchsin S intramuscularly or intravenously and perfusing the knee joints at various intervals to measure the amount of dye passing through the synovial membranes. One knee joint is deprived of its sympathetic innervation, and the other is used as a control. Simultaneously with perfusion, temperatures are taken by means of thermocouples inserted into the lower portions of the quadriceps muscles.

16. Zweifach, B. W.: The Structural Basis of Permeability and Other Functions of Blood Capillaries, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1940, vol. 8, p. 216.

17. Engel, D.: The Influence of the Sympathetic Nervous System on Capillary Permeability, *J. Physiol.* **99**: 161 (Jan.) 1941.

In the majority of both the acute and the long term experiments, in spite of marked vasodilation, excretion of dye was considerably reduced on the sympathectomized side. The amount of dye excreted did not, however, parallel temperature gradients. The author's only explanation for the phenomenon is purely factual, that sympathetic activity increases and sympathectomy decreases capillary permeability. He believes that the permeability factor counterbalances the effect of vasomotor changes.

Menkin¹⁸ shows that an extract of the adrenal cortex is capable of inhibiting the usual effect of leukotaxine, or any inflammatory exudate, in increasing capillary permeability. This effect is easily demonstrated by adding the extract to the exudative material and injecting the mixture into the cutaneous tissue of a normal rabbit. The influence of the substance from the adrenal cortex on capillary filtration is considered by the author of possible significance in various types of shock.

Rigdon¹⁹ suggests that epinephrine also inhibits capillary permeability because trypan blue, administered intravenously, fails to localize in areas of the skin into which epinephrine has been previously injected and which have been treated with xylene. Although it is assumed that the failure of the dye to localize is an index of capillary permeability, it is also possible that complete vascular occlusion or absorption of the dye by the impaired cells may be the primary cause.

Rigdon²⁰ also states that trypan blue injected intravenously into rabbits will localize and concentrate in areas of skin into which a suspension of *Staphylococcus aureus* in physiologic solution of sodium chloride has previously been injected. On the other hand, the dye fails to localize in areas of skin into which killed staphylococci have been injected.

Brown²¹ reports that in a series of 100 persons with scarlet fever the capillary resistance was low at the onset of the disease but increased during convalescence. The persons with the most toxic appearance and those who had most marked desquamation had the lowest capillary resistance. Those who gave a negative reaction to the Dick test also showed a lower capillary resistance. Brown is of the opinion that the increased capillary resistance in patients convalescing from scarlet fever probably due to the decreasing amount of streptococcus toxin in the circulating blood.

18. Menkin, V.: Effect of Adrenal Cortex Extract on Capillary Permeability, *Am. J. Physiol.* **129**:691 (June) 1940.

19. Rigdon, R. H.: A Study of Capillary Permeability and Inflammation in the Skin of Rabbit Given Adrenalin, *Surgery* **8**:839 (Nov.) 1940.

20. Rigdon, R. H.: Observations on Capillary Permeability in Areas of Inflammation Produced by Staphylococci, *Surgery* **9**:436 (March) 1941.

21. Brown, E. E.: Capillary Resistance in Scarlet Fever, *Arch. Pediat.* **57**:553 (Sept.) 1940.

Edwards and his colleagues²² studied the cutaneous vascularity and pigmentation of 4 castrated men (including 1 Negro) and 5 eunuchoid patients. Determinations were made with the Hardy recording spectrophotometer before, during and after treatment with testosterone propionate. The skin of the castrates contained a generally diminished quantity of hemoglobin. The proportionate amount of hemoglobin in a reduced state exceeded that usually noted in the skin of normal men. This variation is interpreted as an indication that the cutaneous vascular bed of castrates, in contrast to that of normal persons, is smaller and has less blood flowing through it. Conversely, in those cutaneous areas characterized by a large venous bed, there was a greater amount of reduced hemoglobin than occurs in normal men, an indication that the veins were dilated. These changes were reversed by the administration of testosterone propionate. In the rich arterial regions of the integument, on the contrary, the volume of blood was increased, and it likewise contained more oxyhemoglobin. The reaction of the testosterone propionate began within one hour after injection and reached a maximum effect in two or three hours. Other results were reported by these authors, but as they are not related to the vascular system they will be omitted. The authors conclude that the androgens have a profound influence on the vascularity and pigmentation of the entire human skin.

Cold.—Brooks and Duncan²³ continue their experimental study of the effect of temperature on the survival of anemic tissue. They attempt to determine the minimum time for applying a pressure of 130 mm. of mercury to a rat's tail maintained at a given temperature which will insure the subsequent development of gangrene after the animal has been returned to room temperature. The apparatus employed is similar to that which the authors have previously described, except for a larger chamber, which permits experiments to be conducted on 8 animals simultaneously, and apparatus for the maintenance of constant temperatures within the range of —5 to 40 C. Gangrene develops more rapidly at higher temperatures. When the tails of 32 rats were surrounded by environmental temperatures between 1 and 5 C. for periods varying from eighteen to ninety-six hours, gangrene did not develop except in 1 tail of the 5 submitted to confinement for ninety-six hours. The latter experiment was not continued beyond this time, as many of the animals died. Gangrene always develops when the tails are exposed to temperatures of —5 C., even without pressure being applied.

22. Edwards, E. A.; Hamilton, J. B.; Duntley, S. Q., and Hubert, G.: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men, *Endocrinology* **28**:119 (Jan.) 1941.

23. Brooks, B., and Duncan, G. W.: Effect of Temperature on Survival of Anemic Tissue: Experimental Study, *Ann. Surg.* **112**:130 (July) 1940.

The authors emphasize that the experiments do not yield sufficient evidence to be accepted for clinical usage, even though gangrene does not occur in all of the animals. Microscopic studies of the rats' tails revealed extensive fibrous replacement of highly specialized tissue. In addition, the rat's tail is thin and cannot be compared to the human extremity, which is relatively thick.

The penetrative effect of cold was studied by Bierman and Friedlander.²⁴ When ice bags were placed on each side of the human calf the surface temperature materially decreased, but the temperature of the calf muscles actually diminished as much as 26.4 F. In this study the thermocouple tip reached about 2 inches (5 cm.) below the surface of the skin. Similar experiments were carried out in other regions of the body. Cold was shown to penetrate through the cheek, from the rectum to the posterior part of the male urethra, from the vagina to the urethra and the bladder and through the abdomen, lowering the temperature of the stomach. Studies on human subjects and on animals show that cold is able to penetrate even through the skull and influence intracranial temperature. The experiments on the systemic effects of cold are well known and are not repeated. The authors make no attempt to explain their observations, nor do they suggest any further therapeutic use of cold. They cite 2 instances in which local refrigeration was applied to the extremities of patients in whom embolization of the iliac arteries occurred as a complication of severe cardiovascular disease. While both of these patients died, the cold prevented the spread of gangrene and cyanosis and thus eliminated the usual fetid odor.

The therapeutic possibilities of reduced temperatures in limb surgery are again stressed by Allen.²⁵ As too few clinical studies have been undertaken, the majority of his conclusions are based on animal experimentation. Refrigeration in treatment of critical conditions is feasible, as the author shows that when cold is applied to a diseased or gangrenous extremity, made bloodless by a tourniquet, the infection or toxemia no longer spreads. Refrigeration will also minimize the use of an anesthetic for future limb surgery. Allen also demonstrates, both clinically and in animal experimentation, that an extremity with normal circulation remains vitalized for a day or two after a tourniquet is applied, providing the environmental temperature is near freezing. In arteriosclerosis obliterans the same thing will occur, but for only a short time.

24. Bierman, W., and Friedlander, M.: The Penetrative Effect of Cold, *Arch. Phys. Therapy* **21**:585 (Oct.) 1940.

25. Allen, F. M.: Reduced Temperatures in Surgery: I. Surgery of Limbs, *Am. J. Surg.* **52**:225 (May) 1941.

Effect of Drugs.—Using a radiometer to measure surface temperatures over various parts of the body, Stewart and Jack²⁶ record the changes in peripheral blood flow resulting from the intravenous injection of theophylline with ethylenediamine. In 21 of 25 cases 0.48 Gm. of the drug induced a transitory rise in blood flow, an effect which could be increased with greater rapidity of injection. As blood flow increased, the cutaneous temperature decreased, mainly because of sweating, and as the skin became cooled the body lost heat. The cutaneous temperature of the hands and feet varies more than that of other parts of the body but is not an index of the average body temperature. Additional studies of the effect of theophylline with ethylenediamine on oxygen consumption and cardiac output revealed that the latter is increased, whereas the former remains unchanged.

Studies of the effect of nicotinic acid on the peripheral circulation have been reviewed previously. Vasodilatation in the extremities was found to be minimal. Recently, Abramson, Katzenstein and Senior²⁷ studied the effect of this substance on the peripheral blood flow by means of the standard plethysmograph. In 15 subjects maintained on well balanced diets, the blood flow increased significantly in the hand and forearm, but only slightly in the leg. Since the changes in peripheral circulation were not accompanied by any definite or consistent alteration in blood pressure or pulse rate, the authors consider it probable that the effect is due to local changes in the blood vessels rather than to an increase in cardiac output.

Bean and Spies,²⁸ who have reported little increase in surface temperature of the extremities, discourage the use of nicotinic acid in the treatment of peripheral vascular disease. They also studied all of the chemicals related to nicotinic acid and found their vasodilating action to be similar. These include the sodium, ammonium, ethyl and monoethanolamine salts of nicotinic acid, as well as pyridine and pyrazine compounds. No vasodilatation followed the administration of certain related pyridine or pyrazine compounds, too numerous to include in this review.

During the past year two new drugs having vasodilating properties were introduced. Unfortunately, neither yields satisfactory results,

26. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, *Am. Heart J.* **20**:205 (Aug.) 1940.

27. Abramson, D. I.; Katzenstein, K. H., and Senior, F. A.: Effect of Nicotinic Acid on Peripheral Blood Flow in Man, *Am. J. M. Sc.* **200**:96 (July) 1940.

28. Bean, W. B., and Spies, T. D.: A Study of the Effects of Nicotinic Acid and Related Pyridine and Pyrazine Compounds on the Temperature of the Skin of Human Beings, *Am. Heart J.* **20**:62 (July) 1940.

being less efficient than those already acceptable. Unna²⁹ studied the antispasmodic action of a new synthetic compound, the hydrochloride of an amino acid ester (benzyl betadimethylaminoalphaphenylalphaethylpropionate hydrochloride), on common laboratory animals and concluded that in its effect on the vascular tree the drug has few advantages over papaverine, other than a lower toxicity. Popkin³⁰ found the new synthetic papaverine-like drug cyverine hydrochloride (di- $[\beta$ -cyclohexylethyl] methylamine hydrochloride) to have a negligible effect on the surface temperature, oscillometric index and clinical improvement of 12 persons suffering from an occlusive vascular disease. In addition, it frequently caused unpleasant symptoms, such as heart burn, headache and dizziness.

Kling³¹ studied the efficiency of histamine, mecholyl chloride (acetyl-betamethylcholine hydrochloride) and doryl (carbaminoylcholine chloride) as vasodilators, using two methods of application. Employing the triple response method described by Lewis, he reports that a 1:1,000 solution of histamine phosphate gives a far stronger wheal and flare than a 1:100 solution of either mecholyl chloride or doryl. By cataphoresis, the full effect of histamine is reached within five to ten minutes, and at that time the rise in the temperature of the skin is greater than that induced by mecholyl. On the other hand, when the treatment is prolonged a somewhat higher and more protracted duration of rise in cutaneous temperature follows cataphoresis of mecholyl because of the more pronounced systemic reaction. Kling considers the latter reaction undesirable, and possibly dangerous. The fact that doryl can induce even a greater systemic reaction makes it unsuitable for iontophoresis. It is the author's opinion that histamine is the drug of choice for the production of local vasodilatation without systemic reaction.

Behnke and Willmon³² show that helium is capable of diffusing inward through the skin at a rate increasing with temperatures in the range of 28 to 35 C. Above 28 C. the increase in absorption of helium is easily correlated with the rise in peripheral blood flow. Computation of

29. Unna, K.: A Pharmacological Study of a New Synthetic Anti-Spasmodic, Benzyl B-Dimethylamino-Phenyl-Ethyl-Propionate Hydrochloride, *J. Pharmacol. & Exper. Therap.* **70**:179 (Oct.) 1940.

30. Popkin, R. J.: Cyverine Hydrochloride, a New Synthetic Papaverine-Like Compound: A Report on Its Vasodilator Action in Chronic Occlusive Peripheral Vascular Diseases, *J. Pharmacol. & Exper. Therap.* **71**:320 (April) 1941.

31. Kling, D. H.: Response and Increase in Skin Temperature as Indicators of Efficiency of Vasodilating Drugs by Iontophoresis, *Arch. Phys. Therapy* **21**: 389 (July) 1940.

32. Behnke, A. R., and Willmon, T. L.: Cutaneous Diffusion of Helium in Relation to Peripheral Blood Flow and the Absorption of Atmospheric Nitrogen Through the Skin, *Am. J. Physiol.* **131**:627 (Jan.) 1941.

the flow on the basis of helium transport from the periphery to the lungs gives values of the same order as those computed by Hardy and Soderstrom on the basis of heat lost from the body. In addition, Behnke and Willmon demonstrated that nitrogen is capable of diffusing inward through the skin, but in somewhat less than 50 per cent of the amount of helium absorbed under similar conditions.

Oscillometry.—The value of oscillometry in making a diagnosis of nonpalpable aneurysm of the peripheral artery is reported by Theis.³³ He is of the opinion that an aneurysm should always be suspected whenever a local high oscillometric reading occurs in the presence of lower readings elsewhere in an extremity. In the case reported by Theis, the oscillometric reading at the knee was double that obtained either above or below that point. A diagnosis of popliteal aneurysm was made and later was confirmed from a study of the amputated leg.

Cutaneous Temperature.—Kirklin, Plummer and Sheard³⁴ record an elevated surface temperature of the toes and fingers of patients with high basal metabolic rates. With a reduction in the metabolic rate, induced either by administration of compound solution of iodine U. S. P. or by partial thyroidectomy, the temperature of the toes decreases. Only minor reduction occurs in the temperature of the fingers. Although for many years clinicians have known this to occur, the authors performed these experiments to emphasize further the role of the extremities, particularly of the lower extremities, in the regulation of the dissipation of heat from the body.

ARTERIOSCLEROSIS

Hines and Barker³⁵ present an excellent review on arteriosclerosis obliterans, incorporating a clinical study of 280 cases. They supplement the clinical data with results of a detailed gross and histologic study of the arteries obtained from 32 legs that were amputated because of this disorder. They found that arteriosclerosis occurs predominantly among men between the ages of 50 and 70 years. It is six times as frequent in men as in women. There is no significant difference in racial incidence, 8.3 per cent of the patients being Jews. This is contrasted with the higher incidence of Jews among the patients having thromboangiitis

33. Theis, F. V.: Peripheral Arterial Aneurysm: Diagnosis, Prognosis and Treatment, *Internat. Clin.* **2**:205 (June) 1940.

34. Kirklin, O. L.; Plummer, W. A., and Sheard, C.: Measurements of the Skin Temperatures of the Extremities in Exophthalmic Goiter, Before and After Medical and Surgical Treatment, *Proc. Staff Meet., Mayo Clin.* **15**:774 (Dec. 4) 1940.

35. Hines, E. A., and Barker, N. W.: Arteriosclerosis Obliterans: A Clinical and Pathological Study, *Am. J. M. Sc.* **200**:717 (Dec.) 1940.

obliterans. The authors emphasize the possible etiologic role of certain metabolic and chemical disturbances, particularly deranged metabolism of fat and cholesterol. The lesions found in the arteries which were examined for pathologic changes consist essentially of three components: (1) atheromatous plaques in the subintimal tissue; (2) degenerative changes in the medial coat, and (3) thrombosis. No significant difference is noted in the lesions of arteriosclerosis obliterans in diabetic patients and those occurring in nondiabetic patients. No direct relation is noted between the extent of calcification and thrombosis with occlusion. On the other hand, a marked difference in the frequency of calcification exists between the sexes. The incidence of calcification among men is 69 per cent and among women 31 per cent. Comments on diagnosis and treatment are made, most of which have been included in previous reviews.

While studying the effect of spasm on the arteries in ergot poisoning, Kaunitz³⁶ noted the similarity of the pathologic changes to those seen in cases of arteriosclerosis. From this he postulates that angiospasm plays an etiologic role in the production of arteriosclerosis. The relation between hypertension and arteriosclerosis is well known, but Kaunitz suggests that perhaps the angiospasm which produces the hypertension also produces the arteriosclerosis. Specimens of the vessels in cases of fatal ergotism are shown to have several features in common with arteriosclerotic vessels. It is the author's opinion that the spasm of the vessel compresses the vasa vasorum and mural lymph spaces and that the compression, if prolonged, may interfere with the nourishment to the vessel wall and lead to degenerative changes, such as hyalinization, fibrosis and atheromatous degeneration characteristic of arteriosclerosis.

The effect of high protein diets and vitamins on experimental atherosclerosis of rabbits was recently reported. Flexner, Bruger and Wright³⁷ state that thiamine hydrochloride and ascorbic acid do not influence the cholesterol content of the blood of rabbits fed cholesterol and that these vitamins neither enhance nor inhibit cholesterol atherosclerosis of the aorta. Meeker and Kesten,³⁸ in studying the effect of protein on experimental atherosclerosis, noted that a high protein diet containing soybean flour diminishes the incidence and degree of experimental sclerosis in rabbits fed cholesterol, whereas a high protein diet containing defatted

36. Kaunitz, J.: Importance of Angiospasm in Development of Arteriosclerosis, *M. Rec.* **152**:106 (Aug. 7) 1940.

37. Flexner, J.; Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: Effect of Thiamine Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits, *Arch. Path.* **31**:82 (Jan.) 1941.

38. Meeker, D. R., and Kesten, H. D.: Effect of High Protein Diets on Experimental Atherosclerosis of Rabbits, *Arch. Path.* **31**:147 (Feb.) 1941.

casein increases the degree of sclerosis. In rabbits given the high protein, defatted casein diet alone hypercholesteremia and atheromatous lesions of the aorta developed, indistinguishable from those produced by cholesterol alone.

Keith and Horton³⁹ report 3 cases of intermittent claudication associated with sclerotic lesions of the abdominal aorta. The site of pain in these cases was chiefly the upper part of the legs and the hips; pain was initiated by walking and was relieved by a short period of rest. In all 3 cases the authors were able to demonstrate arteriosclerotic changes in the abdominal aorta, decrease or absence of pulsations in the arteries of the involved legs and abnormal thermal responses in the toes to changes in environmental temperature.

THROMBOSIS AND EMBOLISM

Lowenberg⁴⁰ reports 3 cases of acute traumatic arterial thrombosis. In each case the involvement was unilateral, was of sudden onset and occurred in a person who was previously healthy and had none of the usual prodromal symptoms of arterial insufficiency. It is Lowenberg's opinion that chronic trauma produces a latent arteritis which acts as the predisposing cause. This was particularly true in 2 of the cases, but in the third one trauma occurred thirty years prior to the onset of thrombosis. In all cases the degree of vasospasm was high, but later, after the patients became asymptomatic, examination revealed definite arterial obliteration.

Gangrene as a complication of scarlet fever is rather rare. Breen⁴¹ and Hoyne and Smollar⁴² each report a case in a 4 year old child. In the case described by the last-named authors panarteritis of most of the arterioles was noted in the pathologic specimen.

A case of gangrene of the hand following the intravenous administration of neoarsphenamine is reported by Newman and Giles.⁴³ A study of the vessels in the amputated extremity revealed complete occlusion of the radial, ulnar and interosseous arteries but no abnormality of the vessels proximal to those involved. The drug had probably been administered into the brachial artery.

39. Keith, N. M., and Horton, B. T.: Intermittent Claudication Associated with Sclerotic Lesions of the Abdominal Aorta, *Internat. Clin.* **2**:21 (June) 1940.

40. Lowenberg, E. L.: Acute Traumatic Arterial Thrombosis of the Extremities, *Virginia M. Monthly* **67**:630 (Oct.) 1940.

41. Breen, G. E.: Gangrene in Scarlet Fever, *Lancet* **2**:196 (Aug. 17) 1940.

42. Hoyne, A. L., and Smollar, L.: Gangrene as a Complication of Scarlet Fever: Report of a Case with Panarteritis, *J. Pediat.* **18**:242 (Feb.) 1941.

43. Newman, L. H., and Giles, H. D.: Case Report of Gangrene of the Hand Due to Neoarsphenamine Injection, *Ohio State M. J.* **36**:961 (Sept.) 1940.

Kaufman⁴⁴ reports a case of gangrene of the finger following digital nerve block anesthesia. Although this complication of local anesthesia is not unknown among surgeons, few cases have been noted in the literature. Little is known of its cause. The author suggests that its prophylaxis is possible and lays special stress on avoiding the use of epinephrine and the tourniquet.

Two cases of gangrene of unknown cause were reported by Marshall.⁴⁵ In both cases the ears, fingers and toes were involved. In 1 case the patient was a man aged 53 and in the other a boy aged 5. Both recovered.

Leriche⁴⁶ describes a syndrome occurring with an occlusion of the terminal portion of the aorta by thrombosis. It is characterized by five symptoms: loss of penile erection; extreme lassitude and fatigability of both lower extremities; complete atrophy of both lower extremities; pallor of the skin of the feet and legs even during dependency, with an ivory or marble appearance during elevation, and the absence of pulsations in the leg and thigh. As a rule the toes maintain a good appearance, and the nails and skin show little evidence of nutritional dysfunction. Cyanosis of the feet and legs occurs in the terminal phases, with desquamation of the skin, ulcer formation at points of pressure, usually preceded by ecchymosis, and, ultimately, gangrene with extreme pain. The diagnosis can be confirmed by arteriographic examination. Leriche includes in his description reports of 2 cases of aortic occlusion.

Many other cases of thrombosis of the abdominal aorta were reported during the past year. Of these, 2 are of interest. Brewster⁴⁷ reports a case in which the aorta was obstructed by a saddle thrombus associated with obstruction of the inferior vena cava by an enlarged mass of malignant lymph glands. In the case reported by Ronald and Leslie⁴⁸ "regional" signs and symptoms were absent. At autopsy no clinical evidence of impaired circulation in the extremities or evidence of collateral circulation could be found.

44. Kaufman, P. A.: Gangrene Following Digital Nerve Block Anesthesia: Report of a Case, *Arch. Surg.* **42**:929 (May) 1941.

45. Marshall, R.: Two Cases of Peripheral Gangrene of Unknown Origin, *Brit. M. J.* **1**:886 (June 1) 1940.

46. Leriche, R.: De la résection du carrefour aortico-iliaque avec double sympathectomie lombaire pour thrombose artéritique de l'aorte; le syndrome de l'oblitération termino-aortique par arterite, *Presse méd.* **48**:601 (July 24-27) 1940.

47. Brewster, E. S.: Obstruction of the Abdominal Aorta and the Inferior Vena Cava Due to "Saddle Thrombus" and Tumor Mass Respectively, *J. Iowa M. Soc.* **31**:12 (Jan.) 1941.

48. Ronald, J., and Leslie, M.: Thrombosis of the Abdominal Aorta, *Glasgow M. J.* **84**:7 (July) 1940.

Koucky and his associates⁴⁹ attempt to evaluate various therapeutic measures employed in 25 cases of peripheral arterial embolism in a large charity hospital. Only statistical data will be mentioned at this time, as the therapeutic measures are considered more fully in the surgical section of this review. Most of the cases of embolism occurred in late adult life. In 2 cases the patients were less than 10 years of age, and in 2 others they were between 70 and 80 years. In this series, mitral heart disease, on the basis of subacute bacterial or chronic rheumatic carditis, was the direct etiologic agent. The lower extremities were more frequently involved than the upper ones, the ratio being 5:1.

THROMBOANGIITIS OBLITERANS

Tetelbaum⁵⁰ employed arteriography in studying 31 cases of thromboangiitis obliterans. This method permits him to determine the degree of narrowing of the arterial lumen, the localization of the constriction and the state of the collateral vessels. It is his opinion that in no other way can the level of the thrombosing process and the degree of the development of the collateral circulation be determined. In some cases he was able to substitute sympathectomy for amputation. If amputation is indicated, the arteriograph will suggest the optimum level. The author urges recourse to arteriography in cases of difficult differentiation between functional and organic disease of the blood vessels.

Theis and Freeland⁵¹ studied the effect of tobacco smoking on the oxygen saturation of the arterial blood in patients with thromboangiitis obliterans and in normal subjects. They noted that smoking is usually accompanied by a greater reduction in the oxygenation of the arterial blood in the former group than in the latter. The extent of reduction seems to be influenced by physiologic adjustments in the blood pressure, pulse rate and peripheral cutaneous temperature. When no adjustment occurs the oxygen saturation of the arterial blood is occasionally found to be elevated. The increased oxygenation is greatest in patients who have recovered from thromboangiitis obliterans and who, after a period of abstinence from smoking, have extremely low oxygen saturation.

It is the author's suggestion that the etiologic factor in thromboangiitis obliterans may be a failure of physiologic adjustment to compensate for the lowered oxygen tension in the tissues.

49. Koucky, J. J.; Beck, W. C., and Hoffman, J. M.: *Peripheral Arterial Embolism*, *Am. J. Surg.* **50**:39 (Oct.) 1940.

50. Tetelbaum, E. G.: *Arteriography in Obliterating Thrombo-Angiitis*, *Vestnik khir.* **59**:464 (May) 1940.

51. Theis, F. V., and Freeland, M. R.: *Smoking and Thrombo-Angiitis Obliterans*, *Ann. Surg.* **113**:411 (March) 1941.

A case of thromboangiitis obliterans involving the spermatic arteries was reported by Mathé.⁵² The thrombosis produced an anemic infarct of the central segment of the testis, resulting in a swelling indistinguishable on physical examination from a tumor.

ARTERITIS

Warshawsky⁵³ reports a case of doubtful syphilitic endarteritis obliterans in a young man with involvement of all extremities and gangrene of one toe. In spite of adequate antisiphilitic therapy, recovery took place in the usual time for any obliterative lesion. As a biopsy was not performed, a procedure most essential for diagnosing this condition, we believe that this case is indistinguishable from one of thromboangiitis obliterans.

A case of mycotic aneurysm of the femoral artery is reported by Schäfer.⁵⁴

During the past year cases of temporal arteritis were reported by Bowers,⁵⁵ Sprague and MacKenzie⁵⁶ and Scott and Maxwell.⁵⁷ A total of 18 cases is now on record. In the case reported by Bowers, prompt relief followed the removal of a segment for biopsy. He considers this significant, as relief was probably obtained by interrupting the sympathetic nerve pathway.

TUMORS OF BLOOD AND LYMPH VESSELS

Watson and McCarthy⁵⁸ made a study of 1,056 patients with 1,363 benign tumors of lymph and blood vessels, including 1,308 hemangiomas, 41 lymphangiomas and 14 hygromas. Evidence of a tumor was present in 73 per cent of the patients at birth and developed in 85 per cent before the end of the first year. The authors propose the following classification of hemangiomas, based on clinical, pathologic and therapeutic considera-

52. Mathé, C. P.: Thrombo-Angiitis Obliterans (Buerger's Disease) of the Spermatic Arteries: Report of a Case, *J. Urol.* **44**:768 (Dec.) 1940.

53. Warshawsky, H.: Syphilitic Endarteritis Obliterans, *M. Bull. Vet. Admin.* **17**:421 (April) 1941.

54. Schäfer, A.: Kriegschirurgische Beobachtung eines mykotischen Aneurysma der Arteria femoralis, *Zentralbl. f. Chir.* **68**:6 (Jan. 4) 1941.

55. Bowers, J. M.: Arteritis of the Temporal Vessels, *Arch. Int. Med.* **66**:384 (Aug.) 1940.

56. Sprague, P. H., and MacKenzie, W. C.: A Case of Temporal Arteritis (Horton-Magath Syndrome), *Canad. M. A. J.* **43**:562 (Dec.) 1940.

57. Scott, T., and Maxwell, E. S.: Temporal Arteritis: A Case Report, *Internat. Clin.* **2**:220 (June) 1941.

58. Watson, W. L., and McCarthy, W. D.: Blood and Lymph Vessel Tumors, *Surg., Gynec. & Obst.* **71**:569 (Nov.) 1940.

tions: capillary hemangioma; cavernous hemangioma; angioblastic, or hypertrophic, hemangioma; racemose hemangioma; diffuse systemic hemangioma; metastasizing hemangioma; naevus vinosus, or port wine stain, and hereditary hemorrhagic telangiectasis (Rendu-Osler-Weber disease). Lymphangiomas, like hemangiomas, may possess marked capacity for growth and are not, as was once supposed, dilated static normal lymph channels. Of the 41 lymphangiomas, 61 per cent were present at birth and 95 per cent were observed before the age of 10. Tumors of this type have been classified into five divisions: simple lymphangioma; cavernous lymphangioma; cellular, or hypertrophic, lymphangioma; diffuse systemic lymphangioma and cystic hygroma, or cystic lymphangioma. The tumor definitely develops from lymphatic tissue in the neck, axilla, retroperitoneal tissues or groin. Hygromas are generally present at birth and grow rapidly. Thirteen of the fourteen tumors of this type were located in the neck; the other one was in the axilla.

Cases of glomus tumors were reported by Raisman,⁵⁹ Hoffmann and Ghormley,⁶⁰ Kirby,⁶¹ Swenson⁶² and Lucinescu, Repciuc and Diaconescu.⁶³ The largest group of cases is reported by Raisman, who found 12 tumors in 11,000 pathologic specimens examined over a period of seven years.

PERIARTERITIS NODOSA

As several hundred cases of periarteritis nodosa are now recorded in the medical literature, we are of the opinion that additional case reports are unnecessary.

An excellent review of periarteritis nodosa is submitted by Grant.⁶⁴ In addition to reporting 7 cases, he suggests that the condition is much less rare than is commonly thought and is not necessarily fatal. Grant believes that if one is to familiarize himself with the general features of the disease, a diagnosis can be made in many instances at the bedside. Unfamiliarity with the disease probably accounts for its assumed rarity.

59. Raisman, V.: Glomus Tumors (Angio-Neuro-Myoma), *Bull. Hosp. Joint Dis.* **1**:107 (Oct.) 1940.

60. Hoffmann, H. O. E., and Ghormley, R. K.: Glomus Tumor and Intramuscular Lipoma: Report of Two Cases, *Proc. Staff Meet., Mayo Clin.* **16**:13 (Jan. 2) 1941.

61. Kirby, D. B.: Neuromyoarterial Glomus Tumor in Eyelid, *Arch. Ophth.* **25**:228 (Feb.) 1941.

62. Swenson, R. E.: Glomus Tumor: Report of Case, *New England J. Med.* **223**:1057 (Dec. 26) 1940.

63. Lucinescu, E.; Repciuc, E., and Diaconescu, M.: Ueber Glomustumoren, *Zentralbl. f. Chir.* **68**:312 (Feb. 15) 1941.

64. Grant, R. T.: Observations on Periarteritis Nodosa, *Clin. Sc.* **4**:245 (Oct.) 1940.

Lebowich and Hunt⁶⁵ stress the significance of eosinophilia accompanied by leukocytosis as a diagnostic feature in periarteritis nodosa. This combination is usually noted during the course of the disease.

CIRCULATION AND ARTHRITIS

Phemister⁶⁶ again cites instances of changes in bones and joints resulting from interruption of circulation. As these changes were non-traumatic in origin, an attempt was made to ascertain the cause. In 2 cases, of which only 1 was described in detail, the bone infarcts were secondary to caisson disease. This diagnosis was confirmed by surgical excision. In another case, an old calcified infarct of the tibia was noted in a patient with advanced arteriosclerosis, on whom autopsy was performed. While there was no direct proof that arteriosclerosis was the cause of the infarction, it appears to be the most plausible explanation. Phemister reports 2 cases in which bone infarct and chronic hypertrophic arthritis, both apparently of long standing, occurred simultaneously and suggests that an etiologic relation exists between the two conditions. He also reports 2 other cases, in which he considers some type of vascular insufficiency capable of producing, in one case, aseptic necrosis in the head of the femur and, in the other, necrosis of the lunate bone.

Steinbrocker and Samuels⁶⁷ evaluated the arterial circulation of the lower extremities in patients with chronic arthritis. Their results were not unlike those noted by many previous investigators, namely, that little relation exists between the location of the arthritic process and the site of the vascular disturbance. Some vascular abnormalities, usually vasomotor in nature, occurred in 65.9 per cent of all patients suffering from rheumatoid arthritis, but in only 35.2 per cent of all patients with osteoarthritis. The high incidence of vasomotor disturbances was considered to be secondary to some systemic reaction, probably acting through the sympathetic nervous system, although in some cases a local reflex vasospastic mechanism in the painful arthritic extremity could not be ruled out.

In a control group of 86 patients with advanced organic arterial disease, 32 per cent had a history, physical signs or roentgenographic evidence of rheumatic or arthritic involvement at some time. This incidence approximates that of such ailments in similar age groups of

65. Lebowich, J., and Hunt, H. D.: The Diagnostic Significance of Eosinophilia in Periarteritis Nodosa, *Am. J. Clin. Path.* **10**:642 (Sept.) 1940.

66. Phemister, D. B.: Changes in Bones and Joints Resulting from Interruption of Circulation: II. Nontraumatic Lesions in Adults with Bone Infarction; Arthritis Deformans, *Arch. Surg.* **41**:1455 (Dec.) 1940.

67. Steinbrocker, O., and Samuels, S. S.: The Arterial Circulation of the Lower Extremities in Chronic Arthritis, *J. Lab. & Clin. Med.* **26**:974 (March) 1941.

persons without arterial disturbances and contributes clinical evidence that pronounced arterial disease alone does not usually produce arthritic signs and symptoms.

RAYNAUD'S DISEASE

Three fatal cases of Raynaud's disease with scleroderma are reported by Linenthal and Talkov.⁶⁸ Roentgenograms revealed areas of fibrosis in the bases of both lungs. The authors suggest that the pulmonary fibrosis was secondary to changes in the small vessels of the lungs as a part of Raynaud's disease and was a demonstration of the generalized arterial involvement which may occur in this disease. Unfortunately, they were unable to demonstrate the pathologic changes, as postmortem examination was not permitted in any of the 3 cases.

Johnson⁶⁹ studied the clinical manifestations and results of treatment in 22 patients with Raynaud's symptoms. His observations on this series of patients confirm Hutchinson's statement, made fifty years ago, that what is known as Raynaud's disease is not a clinical entity and that the peripheral manifestations observed are merely symptoms of some more fundamental disease. This point of view is illustrated by the successful management of several patients by treating such coexisting conditions as anemia or syphilis. In 1 case the attacks completely disappeared after the patient's mental anxiety was relieved. In 5 cases various surgical procedures performed on the sympathetic nervous system were therapeutic failures, whereas in a few of them medical management gave considerable relief. In those patients undergoing surgical treatment, the cutaneous temperature remained elevated, but the symptoms continued. Thermal studies following nerve block revealed that the vessels were fully capable of further dilatation.

Johnson reviewed the various opinions regarding the nature and cause of the vascular phenomena observed in attacks of Raynaud's disease. This difference in opinion is recognized in the modes of treatment, which continue, none too successfully. He introduces a new opinion based on the assumption that the vascular changes are not necessarily due to active vascular constriction, but that they may be the result of vasodilatation in the palmar arch, with a diversion of blood from the fingers and a passive collapse of the digital vessels. In support of this idea he presents many data, the most notable of which are as follows: (1) During an attack of Raynaud's disease the radial pulse remains unchanged; (2) a vasodilating drug, such as amyl nitrite, can produce vasodilatation in one place and passive vasoconstriction in another, pro-

68. Linenthal, H., and Talkov, R.: Pulmonary Fibrosis in Raynaud's Disease, *New England J. Med.* **224**:682 (April) 1941.

69. Johnson, C. A.: A Study of the Clinical Manifestations and the Results of Treatment of Twenty-Two Patients with Raynaud's Symptoms, *Surg., Gynec. & Obst.* **72**:889 (May) 1941.

viding it causes sufficient diversion of blood to one area with a continued fall in blood pressure, and (3) after a median nerve block at the wrist, vasodilatation is known to occur in the first three fingers, to be slight in the fourth and usually to decrease in the fifth, with a fall in the cutaneous temperature of the last-named finger.

VASOSPASTIC DISORDERS

That the autonomic nervous system has representation in the cerebral cortex is suggested by Pilcher, Wyatt and Carney.⁷⁰ They observed a patient who had spastic right hemiplegia, with absence or diminution of pulsations in all of the major arteries on the involved side. The blood pressure and oscillometric index were also lowered on that side. Surgical treatment was advised, and at the time of operation an extensive cerebral infarction was found, involving a major portion of the distribution of the left middle cerebral artery. Continued observations on various autonomic functions showed evidence of unilateral overactivity of the sympathetic nervous system.

An excellent review of the available literature on cervical rib is presented by Holling,⁷¹ with special reference to the theories of causation of symptoms. It is his opinion that the vascular symptoms are secondary to the damage of the arterial wall by the cervical rib. From his own observations and from those of other authors he concludes that the subclavian artery is compressed by the cervical rib at the lateral border of the scalenus anticus or between the anterior end of the rib and the clavicle. In 2 of the cases he reports the latter phenomenon was noted at operation. In a third case the patient had no vascular symptoms but desired relief from a peculiar clicking noise in her shoulder. At the time of operation it was noted that when the arm was adducted the clavicle slipped over the expanded anterior end of the rib with a loud click. The subclavian artery escaped compression because of its unusual lateral position. In all 3 cases relief was obtained after the cervical rib was removed.

Belgrano⁷² studied 31 cases of cervical rib and 6 of hypertrophy of the transverse process of the fourth cervical vertebra. In 30 cases the patients were females, and in 7 they were males. Trauma was the cause in 6 cases. Vascular or neurologic manifestations were present in 25 cases. The most frequent symptoms were unilateral or bilateral pain

70. Pilcher, C.; Wyatt, T. E., and Carney, H. M.: Infarction of the Brain with Unilateral Circulatory Changes, *Arch. Neurol. & Psychiat.* **45**:321 (Feb.) 1941.

71. Holling, H. E.: The Etiology of Vascular Symptoms Occurring in Cases of Cervical Rib, *Guy's Hosp. Rep.* **89**:285, 1940.

72. Belgrano, M.: La costa cervicale, *Gior. veneto di sc. med.* **14**:155 (March) 1940.

in the shoulder and arm, frequently associated with muscular atrophy; cervical pain; paresthesias; variations in local temperature, and other sensory, motor and vascular disturbances. The predominant symptom was acute headache in 1 case and cough in 5 cases. Paresis of the dome of the diaphragm occurred in 3 cases and paralysis of vocal cords in 1 case. The arterial pressure was diminished on the involved side as compared with that on the normal side. In 21 cases roentgenograms revealed the condition was bilateral.

ACROCYANOSIS

The successful treatment of a patient with acrocyanosis by a cervicothoracic sympathetic ganglionectomy indicated to Barker and Baker⁷³ that vasomotor impulses are the dominant factor in the production of arteriolar spasm in this disease. This statement is in contrast to those expressions of belief that the arteriolar spasm in acrocyanosis is intrinsic in the arterioles and that vasomotor impulses play a minor role in provoking the spasm. Not only do the authors present a typical case history, but they suggest an excellent differential diagnosis of this condition, stressing particularly its resemblance to Raynaud's disease and to livedo reticularis.

ACROSCLEROSIS

According to O'Leary and Waisman,⁷⁴ the diagnosis of acrosclerosis is frequently difficult and depends on the onset of the associated vasomotor symptoms. They base their observations on a survey of 64 cases. The syndrome acrosclerosis is a combination of Raynaud's phenomena with secondary scleroderma of the distal parts of the extremities and of the face and neck. These two conditions usually have their onset together, whereas in progressive diffuse scleroderma the onset is associated initially with Raynaud's syndrome and in a few years scleroderma gradually ensues over wide regions of the body. In sclerodactylia, on the other hand, the vasospastic features are initially absent, although they may follow the sclerosis after months or years.

Acrosclerosis occurs preponderantly in women, is usually absent in childhood and is accompanied by vasomotor events which are indistinguishable from manifestations of Raynaud's disease. The treatment is none too successful, but the prognosis with regard to life is favorable. The pathogenesis is only in a stage of hypothesis, as the relation between arterial obstruction and scleroderma is still obscure.

73. Barker, N. W., and Baker, G. S.: Acrocyanosis: Effect of Cervicothoracic Sympathectomy; Report of a Case, *Proc. Staff Meet., Mayo Clin.* **15**:601 (Sept. 18) 1940.

74. O'Leary, P. A., and Waisman, M.: Acrosclerosis, *Proc. Staff Meet., Mayo Clin.* **15**:702 (Oct. 30) 1940.

RETINITIS PIGMENTOSA

Brown and Whitney⁷⁵ studied the peripheral circulation in 9 cases of retinitis pigmentosa and made oscillometric readings and biomicroscopic examination of the capillaries at the nail bed. In all 9 cases the authors found unmistakable evidence of pathologic changes in the peripheral vascular system, from which they concluded a generalized involvement existed. They feel that such capillary abnormality at the chorioretinal threshold is sufficient to produce anoxia and subsequent death of the neuroepithelium. This process could explain the pathogenesis of retinitis pigmentosa.

The authors' criteria for the diagnosis of pathologic involvement of the peripheral vascular system should be criticized. In some cases the only evidence of vascular involvement was tortuous capillary loops in the nail bed, which has previously been shown to be of no diagnostic significance.

AINHUM

Two cases of ainhum, or dactylolysis spontanea, were reported by Gerwig and Warner.⁷⁶ This peculiar disease is characterized by formation of symmetric constricting bands at the bases of the little toes, with gangrene and often spontaneous amputation of the member. It is primarily a tropical disease and occurs chiefly in adult colored males. Its cause is unknown. Pathologically, the constricting band represents proliferation and hyperkeratosis of the surface epithelium, together with fibrosis of the corium. The band appears invariably at the digito-plantar fold. The blood vessels are engorged, especially those distal to the constriction. Ultimately, obliterative endarteritis precedes spontaneous amputation. As the disease is not primarily vascular in origin, the usual therapy is of little value. Intravenous administration of iodides gives relief from pain, but amputation is the treatment of choice. In each of the cases reported by Gerwig and Werner the patient was a southern Negro who had never been out of the United States.

Johnson⁷⁷ describes a case of spontaneous congenital amputation of the fingers and toes, with an annular, ainhum-like band and constriction of the distal portion of the right leg with edema. Roentgenograms of the leg did not reveal any pathologic condition of the bone. The soft tissue had an hourglass appearance, being completely constricted by a fibrous band. Although the peripheral vessels were not palpable, the oscillometric readings were above normal. Rest made the leg smaller, and a

75. Brown, W. M., and Whitney, E. L.: Peripheral Vascular Picture in Retinitis Pigmentosa, *Arch. Ophth.* **24**:984 (Nov.) 1940.

76. Gerwig, W. H., and Warner, C. G.: Ainhum (Dactylolysis Spontanea): Report of Two Cases, *Bull. School Med. Univ. Maryland* **25**:236 (April) 1941.

77. Johnson, H. M.: Congenital Cicatrizing Bands: Report of a Case with Etiologic Observations, *Am. J. Surg.* **52**:498 (June) 1941.

short walk induced slight edema. Excessive walking caused a dull throbbing pain and reappearance of the hourglass contour of the leg. It is interesting to note that the patient, aged 72, had been able to live until recently a normal life, without circulatory embarrassment, and his present condition was probably the result of senility and a weakened vascular bed.

The spontaneous amputation of the digits in his case differs from true ainhum in that the former was congenital. Instances of a similar condition could not be found in an embryologic laboratory which receives many monstrosities and curiosities. The author believes that it probably represents an example of focal necrosis of the limb during the developmental embryonic stage. According to this theory, the damage occurs during the first five weeks of embryonic life, and the residua are apparent at birth. The absence of several fingers and toes may have been the result of focal necrosis in early embryonic life. Other digits had cicatrizing bands but were not spontaneously amputated because this underlying process stopped in time.

SHELTER LEGS

Within a few weeks after the bombardment of London commenced, patients with swollen legs began to consult their physicians in alarming numbers.⁷⁸ Although the swelling appears benign at its onset, it later develops into marked edema, with tense red tender skin, a condition resembling cellulitis. In some cases superficial ulcers and bullae appear, while in others the edema is associated with thrombophlebitis, which usually adds to the confusion in diagnosis. Elderly women seem to be most commonly affected. Carefully taken histories revealed that the majority of patients had been sitting and sleeping in deck chairs for long periods during the bombardment. It is believed that the wooden cross bars on the deck chairs exert a pressure on the back of the thigh or the popliteal vessels that produces a venous stasis. Londoners are informed of the necessity of getting up on their feet for several hours a day as a preventive measure. Once edema develops, it is readily treated by rest in bed.

VENOUS SYSTEM

An exercise test to be used in association with studies on venous pressure is described by Veal and Hussey,⁷⁹ who found it was helpful in distinguishing between a generalized increase in venous pressure, as noted in cases of cardiac failure, and a localized increase in pressure,

78. Shelter Legs, editorial, *Lancet* 2:722 (Dec. 7) 1940.

79. Veal, J. R., and Hussey, H. H.: The Use of "Exercise Tests" in Connection with Venous Pressure Measurements for the Detection of Venous Obstruction in the Upper and Lower Extremities, *Am. Heart J.* 20:308 (Sept.) 1940.

as occurs in cases of venous obstruction. The test is done as follows: With the needle from the venous pressure apparatus inserted into the antecubital or femoral vein, the patient is asked to exercise the hand or foot for one minute. This is best done by having the patient squeeze a roll of bandage placed in the palm of the hand or rise on tiptoe a number of times. In a case of venous obstruction the pressure increases after exercise, whereas in a case of cardiac failure no change is noted, although in both instances the pressure may have been originally elevated.

Ferris and Blankenhorn⁸⁰ note an increase in the venous pressure of the lower extremities in cases of obstruction of the inferior vena cava. A diagnosis of such obstruction is best made by simultaneously measuring the pressure in the veins of the arm and the pressure in the veins of the leg, without the use of exercise. In all 5 cases which the authors report, in which this type of obstruction was known to exist, the venous pressure in the lower extremities was higher than that in the upper.

Using a quantitative histologic method, Carere-Comes and Canna⁸¹ examined morphologically and quantitatively the senile variations in the muscles of the walls of various veins of each of 38 autopsy specimens. Similarities and differences were noted in the muscles of the veins in relation to the regions explored. They noted changes in the various muscle sheaths due to old age and senile atrophy. The muscle of the vein also varies with the sex of the patient. The authors consider that the possible relation between the changes in the muscle of the vein in senility and changes in tonus and venous pressure is plausible.

Tedeschi⁸² notes that with increasing age a fibromuscular thickening appears on the arterial side of the wall of veins running closely adjacent to arteries. This thickening is absent in those veins separated from the companion arteries by the interposition of fatty or fibrous connective tissue and in a vein, such as the subclavian or jugular, which has a course somewhat independent of that of the corresponding artery.

THErapy

Saland⁸³ outlines a plan of treatment for acute arterial occlusions, stressing the importance of suction-pressure therapy. Twenty-nine cases

80. Ferris, E. B., and Blankenhorn, M. A.: Obstruction of the Vena Cava Inferior in Liver Abscess: A New Diagnostic Sign, *Internat. Clin.* **4**:1 (March) 1941.

81. Carere-Comes, O., and Canna, S.: La muscolatura delle vene nelle varie età: Ricerche di istologia quantitativa, *Cardiologia* **4**:283, 1940.

82. Tedeschi, C.: Fibromuscular Thickening in the Walls of Veins Adjacent to Arteries, *Anat. Rec.* **79**:243 (Feb. 25) 1941.

83. Saland, G.: Acute Occlusions of the Peripheral Arteries: Clinical Analysis and Treatment, *Ann. Int. Med.* **14**:2027 (May) 1941.

of major and 2 cases of minor arterial occlusion are reported. Because the author was able to distinguish between occlusions of embolic and those of thrombotic origin certain observations are worthy of repetition. Embolism occurred in younger patients. Sex was not a factor in the causation of occlusion, although diabetes was more prevalent in females. Auricular fibrillation was a frequent precursor of embolism, but not of thrombosis. Heart disease was the underlying condition in 100 per cent of the cases of embolism. This association with heart disease is a major factor in the prognosis, because all 15 deaths in this series of cases were due not to the peripheral vascular disease but to the underlying cardiac condition.

Gangrene developed in all of the 8 cases in which no treatment was instituted except hospitalization and, presumably, rest in bed. In this group amputation was ultimately done in 62.5 per cent of the cases, and the known mortality of all 8 cases was 62.5 per cent. Conservative therapy, consisting of rest in bed, use of reflex heat, papaverine and whisky and pavaex treatments, was given in the remaining 23 cases. In most of the cases a minimum of one hundred hours of suction-pressure therapy was administered. Under this regimen Saland was able to save the limb in 95 per cent of the cases. In the group in which treatment was given the stay in the hospital was twenty and eight-tenths days less, on the average, than that of the group in which no treatment was given.

Moss and Herrmann⁸⁴ were able to control the pain of "night cramps," commonly seen in middle-aged and elderly patients, by the oral administration of quinine sulfate. Fifteen patients were so treated, none of whom had evidence of serious vascular insufficiency. Improvement to the point of complete cessation of pain was noted within a relatively short period. In some cases return of symptoms did not follow cessation of medication or substitution of placebo capsules but in the majority of cases an exacerbation occurred.

Bennett, Hines and Krusen⁸⁵ were able to produce reflex vasodilatation in the extremities by applying short wave diathermy to the trunk. Various methods of application were tried, but the use of the electromagnetic cable in a pancake formation under the lumbosacral region was found to be the most simple and comfortable. Twenty observations were made, and in each instance the lower extremities became warmer. The use of diathermy as a test for vasospasm is dis-

84. Moss, H. K., and Herrmann, L. G.: Use of Quinine for Relief of "Night Cramps" in the Extremities, *J. A. M. A.* **115**:1358 (Oct. 19) 1940.

85. Bennett, R. L.; Hines, E. A., and Krusen, F. H.: Effect of Short-Wave Diathermy on the Cutaneous Temperatures of the Feet, *Am. Heart J.* **21**:490 (April) 1941.

couraged. The authors are aware of the dangers of this form of therapy and suggest that it be used only under careful medical supervision.

Rothberg⁸⁶ treated a patient with Raynaud's disease by roentgen irradiation of the cervical and lumbar regions. Symptomatic relief was noted for two consecutive winters. As the patient had a recurrence of symptoms six months later, additional radiation was given, which allowed her freedom from pain and ulcers for the remainder of the winter.

ABNORMALITIES OF BLOOD PRESSURE

The question as to what constitutes normal blood pressure is still under discussion. The paper by Robinson and Brucer,⁸⁷ which was reviewed last year, has aroused some criticism, particularly in regard to the statistical methods employed in arriving at the conclusions. The author⁸⁸ of the criticism states that his objections do not center about the acceptability to physicians of the conclusions reached, but about the validity of the statistical proof offered.

Robinson⁸⁹ further continues the argument in regard to the "ideal normal blood pressure," which in his opinion is below 110 mm. of mercury systolic and 70 diastolic. Such pressures were found in 25 per cent of 10,833 persons. Thirty-four per cent had diastolic pressures below 70 mm. Pressures of this type had little relation to age until the age of 70 years was reached; then the incidence seemed to decrease. Young women were more numerous in this low pressure group, but the incidence in older women was about the same as that in men of similar age. Weight seemed to be a much more important factor than sex, and persons of light weight, regardless of sex, were more common in the low blood pressure group. Another interesting point noted was that low pressures show less fluctuation; even the yearly variation was less erratic than that of higher pressures. The author insists that low pressure has no characteristic symptomatology. Neither excessive fatigue nor lowered vitality and energy were noted in the low pressure group. In fact, these symptoms were more frequent in the high pressure group. When organic disease is excluded, such low pressure is associated with a mortality rate lower than that for average pressures.

86. Rothberg, A. S.: The Relief of Symptoms in Raynaud's Disease by Roentgen Therapy, *Am. J. Roentgenol.* **45**:412 (March) 1941.

87. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, *Arch. Int. Med.* **64**:409 (Sept.) 1939.

88. Treolar, A. E.: Normal Blood Pressure, *Arch. Int. Med.* **66**:848 (Oct.) 1940.

89. Robinson, S. C.: Hypotension: The Ideal Normal Blood Pressure, *New England J. Med.* **223**:407 (Sept. 12) 1940.

The relation between body build and hypertension has also been studied by Robinson and Brucer.⁹⁰ The controversy in regard to the relation between these factors has not yet been satisfactorily decided. These authors are convinced that one does exist. That is, men and women of broad build show a marked tendency to hypertension. The systolic pressures have a definite tendency to increase directly with the chest/height ratio. While the proportions are not exactly the same in the two sexes, linear build (low chest/height ratio) is much more frequently accompanied by low than by high pressures, both systolic and diastolic. The incidence of high pressure increases with age in men of lateral build. In men of linear (slender) build the incidence of high pressure tends to remain constant up to the seventh decade and the incidence of low pressure is constant throughout life. An increase is also observed in the average build (chest/height ratio) until the age of 50 years. After this age the average build tends to decrease. The authors believe that the chest/height ratio is a much more reliable criterion than weight under these conditions.

Observations made by Thacker⁹¹ on a large group of university students tend to agree with those of others reporting similar work. The arbitrary blood pressure levels used in this study were 108 mm. or less, regarded as hypotensive, and 150 mm. or above, regarded as hypertensive. A control group was used whose pressures ranged from 114 to 138 mm. These three groups were subjected to a variation of the cold pressor test of Hines and Brown. It was found that normal subjects showed a more rapid response in that their pressures reached the maximum in a shorter time and returned to normal more rapidly than did the pressures of hypertensive or hypotensive subjects. Observations of other authors are in essential agreement as far as the reaction of hypertensive subjects to the cold pressor test is concerned. The same factors which are responsible for the emotional state of a person play an important role in the reactions of his blood pressure.

The author also concluded from his observations that there is a definite hereditary factor in the normal regulation of blood pressure. "The tendency toward essential hypertension or hypotension is carried by the germ plasm from one generation to the next." The use of coffee and tobacco has no significant influence on blood pressure levels. He

90. Robinson, S. C., and Brucer, M.: Body Build and Hypertension, *Arch. Int. Med.* **66**:393 (Aug.) 1940. Robinson, S. C.: Hypertension in Relation to Height: Its Variation with Body Build and Obesity, *J. Lab. & Clin. Med.* **20**: 930 (March) 1941.

91. Thacker, E. A.: A Comparative Study of Normal and Abnormal Blood Pressures Among University Students, Including the Cold-Pressor Test, *Am. Heart J.* **20**:89 (July) 1940.

also concluded that elevation of blood pressure should not be considered as hypertension until at least three separate observations have been made.

It has been suggested that the range of variability of blood pressure may be as important as or more important than any single reading in the determining the subsequent status in an individual case. In order to gather further information in this regard Hines⁹² studied the records of 1,522 patients ten and twenty years after the original reading had been obtained. He has been of the opinion that an initial reading made under strange surroundings by a strange physician may have a significance similar to that of a reading made after the cold pressor test, in that it represents a reaction to emotional stress. As a result of these observations the idea is advanced that excessive variability from the usually normal pressure should be considered as evidence of the presence of the hypertensive state. (Hypertension is likely to develop at a later date in persons exhibiting such variability.) While Hines draws no definite conclusions on the basis of this study, he is inclined to believe that hypertension probably will not develop in persons whose pressure rises no higher than 140 systolic or 85 diastolic under nervous stress. On the other hand, persons who show even transient rises above this level are likely to display persistent hypertension subsequently. He also points out that elevation of the systolic pressure alone is not significant, but a rise above 85 diastolic is. These findings seem to hold true regardless of age. Such observations as these are significant and aid in a better understanding of the problem. Thacker⁹³ continued his observations on his group of students by studying the effect of exercise. His results seem to indicate that a standard exercise test yields a fairly consistent response in each of the three blood pressure groups. As a rule the increase in systolic pressure was greater in the hypertensive group than in the other two groups. The variation was considerable. Twenty per cent of the hypertensive subjects had an increase above 60 mm. of mercury, and in 2 per cent it reached 80 mm. The maximum rise for the normal subjects was 50 mm. in 82.7 per cent of cases, and in none was the increase greater than 60 mm. In persons with normal pressure such rises might have the same significance as rises obtained with the cold pressor test. The maximum rise in the hypotensive group was 40 mm., and in 91.6 per cent the rise was less than 30 mm.

The diastolic pressure decreased with exercise in all groups. Ninety-one per cent of the low pressure and normal groups did not show a

92. Hines, E. A., Jr.: Range of Normal Blood Pressure and Subsequent Development of Hypertension: A Follow-Up of 1522 Patients, *J. A. M. A.* **115**: 271 (July 27) 1940.

93. Thacker, E. A.: Blood Pressure Studies on University Students, Including the Effects of Exercise on Essential Hypertension, and Normal Subjects, *Ann. Int. Med.* **14**:415 (Sept.) 1940.

fall of more than 20 mm., and the decrease was usually less. The hypertensive subjects tended to show a greater variation in this respect also.

The return to normal of the systolic pressure occurred more rapidly in the normal than in the other two groups. Pulse rate was not a factor.

These observations are important in that they seem to indicate that the smaller the individual range of blood pressure in both systolic and diastolic levels, the less is the likelihood of hypertension developing later. That is, the lower levels of blood pressure have the least variation, and a short range of variation as the result of any stimulus must be regarded as normal.

This is further indicated by the observation that the usual pressures of the hypertensive subjects were considerably elevated above the basal pressure. Emotional factors, or the factors which govern the emotional status of a person, seem to be important in determining the blood pressure status. This agrees with the views of Hines. There certainly seems to be a hereditary relation in the tendency to high, low or normal pressure, as indicated in Thacker's groups. Work or exercise was not a factor, but increased food intake was common (two and a half times as frequent) in the hypertensive subjects.

Among the factors which result in variation of blood pressure Jacobson⁹⁴ has found that repeated contraction of a muscle group for a period of several minutes followed by complete relaxation is frequently accompanied by rises and falls both in systolic and in diastolic blood pressure. The extent of the rise and fall depends on the intensity of the effort and the ability of the subject to relax completely afterward. No rise may be obtained unless low pressure is previously brought about by complete relaxation. The more extensive the muscle contraction, the greater is the rise in pressure which follows. The author believes that emotional influences are not operative in these phenomena. This work appears to demonstrate another factor, which may be an important influence in the variability both of normal blood pressure and of hypertension.

In order to obviate some of the variations in pressure, particularly those associated with the emotional effect of the actual recording, Ayman and Goldshine⁹⁵ have provided patients with the equipment for determination of their own pressures. Pressures recorded in the clinic were in general considerably higher than those recorded by the

94. Jacobson, E.: Variation of Blood Pressure with Brief Voluntary Muscular Contractions, *J. Lab. & Clin. Med.* **25**:1029 (July) 1940.

95. Ayman, D., and Goldshine, A. D.: Blood Pressure Determinations by Patients with Essential Hypertension: I. The Difference Between Clinic and Home Readings Before Treatment, *Am. J. M. Sc.* **200**:465 (Oct.) 1940.

patient at home; in some cases the difference amounted to as much as 50 to 70 mm. higher in the clinic than at home. In others the difference was not so marked, amounting to only 10 to 15 mm. in the systolic pressure. The maximum differences were noted when the home reading was taken after exercise. The diastolic pressure showed less variation, but in 23 per cent of cases there was a difference of 20 mm. or more, a striking variation. Thus it is seen that the average blood pressure as measured in the office is usually higher than that under conditions in which the patient lives, but represents in general the upper limits of the variation to which each person may be subjected.

These observations have been extended to determinations made after treatment.⁹⁶ It was thought by the writers that response to therapy was indicated by observations made at home when it was impossible to determine any result after the use of some drugs if the pressure was determined by the physician. Apparently the emotional reaction, or pressor response, is greater than the vasodilator effect of the drug. Under the ordinary conditions of the patient's life, the depressor effect may be fairly satisfactory. Apparently the observations of these authors coincide with those of Hines in regard to the emotional effect of mere taking of blood pressure as an effective stimulus which is part of the hypertensive state.

Griffith, Roberts and Corbit⁹⁷ have attempted to classify hypertension on the basis of objective observations. When the capillaries of the skin were studied most of the patients with hypertension fell into the classification of normal, although some were found who exhibited a larger number than normal of capillaries in use in a given area under average conditions. Measurement of the capillary pressure, both in normal skin and in an area of histamine flare, yielded variable results.⁹⁸ Normally, by the method used, a rise of 3 to 13 mm. of mercury occurred in the area of flare. In persons with hypertension, these results were exceedingly variable. A change of less than 3 mm. of mercury after histamine flare was thought to indicate sclerosis of the precapillary arterioles. In some instances there was an exaggerated rise of more than 13 mm. of mercury. In such cases it may be assumed that the precapillary arterioles dilated to allow the marked

96. Ayman, D., and Goldshine, A. D.: Blood Pressure Determinations by Patient with Essential Hypertension: II. The Difference Between Home and Clinic Readings During and After Treatment, *Am. J. M. Sc.* **201**:157 (Feb.) 1941.

97. Griffith, J. Q., Jr.; Roberts, E., and Corbit, H. O.: Studies of Criteria for Classification of Arterial Hypertension: I. Cutaneous Capillaries, *Am. Heart J.* **21**:47 (Jan.) 1941.

98. Griffith, J. Q., Jr.; Roberts, E., and Corbit, H. O.: Studies of Criteria for Classification of Arterial Hypertension: II. Minute Vessel Pressure, *Am. Heart J.* **21**:54 (Jan.) 1941.

increase in pressure from the arterial system to extend into the capillary bed. The cutaneous lymph flow⁹⁹ was found to be normal in most instances of hypertension, but it was increased in a small number of cases. Increased capillary pressure was usually present when the flow of lymph was increased.

Blood volume was most frequently found to be unchanged,¹⁰⁰ but in some instances an increase was noted, in which cases there was also increased capillary pressure or increased lymph flow. Increased blood volume is accounted for either on the basis of decreased vascular tone, particularly in the peripheral bed, or on a metabolic basis, which, according to the authors, indicates an increased amount of water in the blood, due either to added intake or to failure of elimination. The increase in flow in minute vessels and in lymph vessels is a compensating mechanism. Certainly increased blood volume is seldom associated with hypertension.

Griffith and his associates¹⁰¹ have also attempted to evaluate the role of the pituitary gland in hypertension both by experimental observation of animals given extract of the posterior lobe of the pituitary body and by the recovery of pituitary substances from the blood of clinical patients. They found that large doses of pitressin administered to rats produced a rise in blood pressure which reached 200 mm. of mercury or more and endured for several hours. Blood volume was found to be diminished during the period of hypertension. If a single small dose of the extract was given, no change in blood volume was noted, but with repeated small doses a rise occurred. It was thought pressure might be elevated in the minute vessels, although the methods for measurement in the rats are not satisfactory. These observations were largely on cases of the type of pituitary hypertension in which increased blood volume occurred.

In the attempt to demonstrate the presence of pituitary substance in patients with hypertension, a biologic test for the presence of an antidiuretic substance in the serum was employed. The test was positive in some cases of hypertension. In such cases it was found that capillary pressure was increased; in about one half of them the lymph flow increased, and in some papilledema appeared. The blood

99. Griffith, J. Q., Jr.; Roberts, E.; Rutherford, R. B., and Corbit, H. O.: Studies of Criteria for Classification of Arterial Hypertension: III. Cutaneous Lymphatic Flow, *Am. Heart J.* **21**:62 (Jan.) 1941.

100. Griffith, J. Q., Jr.; Rutherford, R. B.; Roberts, E., and Lindauer, M. A.: Studies of Criteria for Classification of Arterial Hypertension: IV. Blood Volume, *Am. Heart J.* **21**:67 (Jan.) 1941.

101. Griffith, J. Q., Jr.; Corbit, H. O.; Rutherford, R. B., and Lindauer, M. A.: Studies of Criteria for Classification of Arterial Hypertension: V. Types of Hypertension Associated with the Presence of Posterior Pituitary Substance, *Am. Heart J.* **21**:77 (Jan.) 1941.

volume was either normal or increased. In such cases it was found that after irradiation of the pituitary body the test became negative and some fall in blood pressure and clinical improvement occurred. The test used in conjunction with irradiation may be considered as a guide to the effect of the process. It has little or no other value.

Graybiel and Glendy,¹⁰² did not find any significant difference in effect on blood pressure in either normal and hypertensive subjects when pitressin was administered slowly by the intravenous route. Increases in pressure were slight. The return of the pressure to the control level was somewhat slower in the hypertensive patients than in the normal ones. The authors observed constriction of the minute vessels and of the large arteries but not of the arterioles.

When the tests devised by Griffith and co-workers were applied in relation to thiocyanate therapy,¹⁰³ it was found that they furnished a fairly reliable guide to the likelihood of success with this type of treatment. If the capillary responses were normal, clinical improvement usually followed. If precapillary sclerosis was suggested by increased capillary pressure and increased lymphatic flow or if papilledema was present thiocyanate therapy usually failed. Therefore it would seem that the location of the effect is on the arteriolar structures, and if organic change in the walls of the arterioles exists release of spasm is unlikely to occur and but little fall in pressure can be expected. In general, the clinical results were as predicted.

When these observations were applied to cases in which papilledema was associated with hypertension,¹⁰⁴ increased intracranial tension, as measured by elevation of the spinal fluid pressure, was found. Increases in the pressure in minute vessels, cutaneous lymph flow and blood volume also occurred. In some cases there was evidence of an anti-diuretic substance in the blood. In some cases renal disease was present.

It is believed that increased formation of cerebrospinal fluid is the cause of the increased intracranial pressure. This increase in quantity cannot be removed sufficiently rapidly by the blood, either because of the presence of the antidiuretic substance or because of renal failure to excrete water.

102. Graybiel, A., and Glendy, R. E.: Circulatory Effects Following the Intravenous Administration of Pitressin in Normal Persons and in Patients with Hypertension and Angina Pectoris, *Am. Heart J.* **21**:481 (April) 1941.

103. Griffith, J. Q., Jr.; Lindauer, M. A.; Roberts, E., and Rutherford, R. B.: Studies of Criteria for Classification of Arterial Hypertension: VI. Treatment with Thiocyanate, *Am. Heart J.* **21**:90 (Jan.) 1941.

104. Griffith, J. Q., Jr.; Fry, W. E., and Roberts, E.: Studies of Criteria for Classification of Arterial Hypertension: VII. Increased Intracranial Pressure and Papilledema, *Am. Heart J.* **21**:94 (Jan.) 1941.

Cases of hypertension in childhood which could not be classified under any of the definitely known groups have been reported by Clark¹⁰⁵ and Sobel.¹⁰⁶ Apparently these cases would fall into the so-called essential hypertensive groups. Sobel points out that intermittent elevation of pressure in childhood tends in some cases to become more frequent and denotes incipient hypertension. In fact, the hypertensive state frequently has its origin in childhood or adolescence.

Corcoran and Page¹⁰⁷ present their views on the correlation of the essential aspects of clinical and experimental hypertension and suggest that angiotonin is involved in the pathogenesis of essential and malignant hypertension in man. The problem is considered from the standpoint of the four essential manifestations of hypertension, namely, those of neurogenic, endocrine, cardiovascular and renal origin. The authors point out that renin of itself is not an angiospastic substance, but when it is activated by a substance present in normal plasma, which is termed renin activator, a strong vasoconstrictor substance, which has been designated angiotonin, is produced. This differs from other vasoconstrictor substances in that it acts principally on the smooth muscle of the arterioles and on the heart. The heart responds by increased activity, particularly in the force of the beat. This response is essential because of the increased peripheral resistance offered by constriction of the arterioles. These two results are its principal effects. Thus, cardiac failure as hypertension progresses is an integral part of the disease pattern. The clinical features are progressive constriction of the arterioles, with thickening of their walls, and hypertrophy of the cardiac muscle. As these processes continue, cellular changes take place; nutrition cannot keep pace; sclerosis occurs, and finally degenerative changes result in failure of the heart, as well as in disturbances in the central nervous system, the retina and, particularly, the kidneys. The course of the disease is greatly accelerated when it is altered by the phenomena which characterize malignant hypertension, manifested pathologically by necrotizing arteriolitis. Angiotonin is believed to be capable of producing this disease pattern, resulting as it does from renal ischemia. It appears that the more rapidly renin is elaborated, the more rapid and severe is the pathologic process in the vessels.

The kidneys in cases of hypertension, as observed clinically and pathologically, follow a similar progression of changes. There is no

105. Clark, H. C.: Hypertension in Early Childhood, *Am. J. Dis. Child.* **59**: 353 (Feb.) 1940.

106. Sobel, I. P.: So-Called Essential Hypertension in Childhood, *Am. J. Dis. Child.* **61**:280 (Feb.) 1941.

107. Corcoran, A. C., and Page, I. H.: Arterial Hypertension: Correlation of Clinical and Experimental Observations, *J. A. M. A.* **116**:690 (Feb. 22) 1941.

apparent early functional disturbance, but its presence is indicated by the increased rate of glomerular filtration of water, as measured by inulin clearance. This increase cannot arise from the elevation of systemic arterial pressure alone and therefore must be due to increased intraglomerular pressure, which in turn is probably the result of constriction of the efferent arterioles. This view is strengthened by the fact that actually the rate of renal blood flow is decreased, another of the characteristic effects of angiotonin. The peculiar increase in glomerular function is responsible for the fact that renal function, as measured by such tests as urea clearance, remains normal in a case of hypertension, even though the disease may be far advanced. Eventually the continued vasoconstriction results in organic changes in the arterioles and occlusion takes place; glomeruli become sclerosed, and finally renal failure supervenes.

The relation of the endocrine system to this mechanism is apparently secondary. The adrenal cortex and the hypophysis are particularly important in that their secretions maintain the cardiovascular system in a state receptive to hypertensive stimuli. It seems probable that the central nervous system may play a dual role in that both reflex and psychogenic factors not only contribute to the maintenance of hypertension but may even be an initiating factor. The characteristic cerebral phenomena of hypertension and the effects of operations on the autonomic nervous system, as well as the effect of psychogenic factors on the clinical course, are offered in support of this view.

That essential hypertension in man, including the malignant variety, has the same essential pathogenesis as experimental hypertension is also indicated by the fact that in both conditions the blood pressure, as well as the clinical symptoms, has been relieved by the administration of the antipressor substance which Page and his co-workers and Harrison and associates have discovered.

This view is further strengthened by the experimental injection and infusion of angiotonin into the veins of human subjects.¹⁰⁸ The rises in blood pressure which followed this procedure were characteristic of clinical hypertension, as well as of experimental hypertension in animals.

It seems probable that persistent hypertension may result from, or at least be associated with, the paroxysmal hypertension caused by a pheochromocytoma of an adrenal gland. Several cases of paroxysmal hypertension have been reported, and emphasis has been placed on

108. Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics by Injection of Angiotonin in Human Beings, *Proc. Soc. Exper. Biol. & Med.* **46**:244 (Feb.) 1941.

the importance of diagnosis, because if this disorder is recognized sufficiently early surgical removal of the tumor may result in complete cure.

Van Epps, Hyndman and Greene¹⁰⁹ comment particularly on the symptomatology. A history of paroxysmal attacks of peculiar sensations may be the only subjective manifestation. The sensations may be located in the neck, the epigastrium or the substernal region. The sensation may be one of fullness, swelling, choking or pressure in the chest suggesting angina pectoris. Pain in the epigastrium, such as sometimes occurs in cases of peptic ulcer, may be the outstanding symptom. Angiospasm of the extremities or the tip of the nose is also described. Some of the other characteristic symptoms are a rise in both systolic and diastolic pressures, pallor, tremor, headache, vertigo and cardiac palpitation. The duration of paroxysms may vary from a few minutes to forty-eight hours.

Brunschwig and Humphreys¹¹⁰ emphasize the presence of syncope, an increase of 100 mm. in the systolic pressure and a marked rise in the diastolic pressure. It has been assumed that the attacks are due to the liberation of epinephrine or epinephrine-like substances from the tumor. The attack seems to be often initiated by trauma, by motion in a certain direction, such as bending or stooping, or even by emotional strain.

Attempts to visualize the tumor, even by means of the perirenal insufflation of air or oxygen, often fail. If such a measure is attempted, it would appear that oxygen is much the safer substance to employ. Considerable difficulty and even dangerous symptoms have resulted from the use of air. In 1 case reported by Brunschwig and Humphreys no actual tumor involving an adrenal gland was found, although the symptoms were typical. In such a case it is possible that a tumor arising from a secondary adrenal rest in any of various locations might be responsible. Under such circumstances location of the tumor would be exceedingly difficult.

Confirming results of previous similar studies, Odel¹¹¹ states that malignant hypertension must be regarded as a diffuse arteriolar disease and that no organ can escape the effects of the rise in blood

109. Van Epps, E. F.; Hyndman, O. R., and Greene, J. A.: Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of Adrenal, *Arch. Int. Med.* **65**:1123 (June) 1940.

110. Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, *J. A. M. A.* **115**:355 (Aug. 3) 1940.

111. Odel, H. M.: Structural Changes in the Arterioles of the Myocardium in Diffuse Arteriolar Disease with Hypertension on Group Four, *Arch. Int. Med.* **66**:479 (Sept.) 1940.

pressure. Structural changes in the arterioles have been demonstrated, particularly in the brain, kidneys and myocardium. Odel found that structural changes in the arterioles of the heart apparently do not progress at the same rate or to the same degree as do similar changes elsewhere in the body. Change was observed primarily in the arterioles of the myocardium. The nature, and even the degree, of alteration in these structures varied widely. Increase in the nuclei of the media seems to occur early. Hyperplasia of the internal elastic layer, proliferation of the intima and degenerative changes follow much later. In some instances no arteriolar change was noted, even though it was relatively marked in other organs.

Both the pathogenesis and the experimental study of renal hypertension have been considered in a review by McCann.¹¹² He has included the essential reports on the presence of pressor substances arising from renal ischemia, as well as on the presence and defects of a depressor substance. He has also discussed clinical hypertension from the standpoint of urologic diseases. This phase of the problem is therefore not included in this review.

HYPOTENSION

Stead and Ebert¹¹³ describe postural hypotension as a disease of the sympathetic nervous system. Three cases of the typical form were carefully studied. Syncope, weakness, loss of consciousness and vertigo in the upright position or after exercise were the outstanding symptoms. Sometimes rather vigorous exercise seemed to be necessary to induce an episode. One man was unable to shave while standing because of tremor and ataxia. In a standing position his arterial pressure fell to 58 mm. or lower in the systolic phase. In a horizontal position, the blood pressure of another patient averaged 90 systolic and 60 diastolic in the morning, while in the afternoon it was always higher, averaging 160 systolic and 95 diastolic. In the upright position the pressure dropped to 50 mm. or lower, while the heart rate increased 30 to 40 beats per minute. This variation of pressure at different times of the day was noted in 2 of the 3 cases. It is interesting that no signs or symptoms of impaired cerebral function occurred unless the pressure fell to 50 mm. of mercury systolic or less. The initial symptoms were pallor, blurring of vision, tremor of the hands and inability to understand commands. Clonic movement of the arms and legs occurred. There was no recollection of the events which took place during such an

112. McCann, W. S.: Bright's Disease: A Review of the Recent Literature, *Arch. Int. Med.* **67**:680 (March) 1941.

113. Stead, E. A., and Ebert, R. V.: Postural Hypotension: A Disease of the Sympathetic Nervous System, *Arch. Int. Med.* **67**:547 (March) 1941.

episode. Nausea, sweating and slow pulse rate do not occur in this type of syncope, as they do in the ordinary type of fainting or in that associated with increased carotid sinus reflex irritability. The essential defect determined by the writers from their observations in these 3 cases was a failure of the normal response to change in posture. No more blood is pooled in the lower parts of the body on standing than there is in normal subjects under similar conditions. The pooling of the normal amount of blood causes an abnormal fall in blood pressure through the failure of the normal reflex. The location of the defect in the sympathetic nervous system is not apparent from these studies, although it would seem that whatever defect existed might involve the central portions of the sympathetic mechanism rather than peripheral elements of the reflex arc. If the lesions are extensive, other manifestations of loss of sympathetic function, such as disturbances in sweating, temperature of the body and heart rate, might be expected. In view of the evidence from these studies, it might well be supposed that postural hypotension would occur after extensive sympathectomy for the relief of hypertension. Although postural changes in pressure under similar conditions have been previously reported, the earlier descriptions of symptoms have not approached that presented by these authors.

A CRITICAL REVIEW OF THE SURGICAL TREATMENT

BY DR. DE TAKÁTS AND DR. JESSER

PARAVERTEBRAL BLOCK

Because of the widespread use of alcohol injections into the sympathetic trunk or ganglions, Merrick's¹¹⁴ study of the degeneration and recovery of autonomic neurons following alcohol block deserves considerable interest. The author injected 95 per cent alcohol into cats, either by the customary paravertebral approach or directly into the ganglion or ramus. The changes which occur after infiltration of a ganglion differ from those which follow when the ramus is infiltrated. Injection into a ganglion produces a permanent block to all the post-ganglionic fibers taking origin from it, since the alcohol kills the ganglion cells. After thirty-five days nothing remains but a connective tissue scar. In order to obtain this result, however, the alcohol must be injected into the ganglion or in its close vicinity. When the ramus is infiltrated the alcohol dissolves the myelin sheath and interrupts the continuity of the axon, so that the distal segments undergo typical wallerian degeneration. Retrograde changes also occur in cell bodies

114. Merrick, R. L.: Degeneration and Recovery of Autonomic Neurons Following Alcoholic Block, *Ann. Surg.* **113**:298 (Feb.) 1941.

proximal to the injection. While the nerve elements may be completely destroyed, the fibrous elements of the ramus maintain its continuity. Blocking of this type is less permanent than that obtained by rami-section. The fibers penetrate the scar easily, and function is reestablished. Regeneration of myelin was apparent in ninety days. In one hundred and seventy days function was restored through a preganglionic fiber blocked with alcohol.

The author points out that permanent block of the sympathetic impulses to the abdominal viscera by means of such injections is impossible, since most of the neurons from which postganglionic fibers to these organs are derived are located in the prevertebral ganglions. On the other hand, permanent and complete block of sympathetic impulses to the thoracic viscera or the extremities may be produced by paravertebral injection, since infiltration of the ganglions destroys the cells of the postganglionic fibers.

This work explains why in certain cases alcohol block has only an evanescent effect, even though complete paralysis of the sympathetic nerves is obtained at the time of injection. It also indicates that surgical sympathectomy, whenever the patient's condition permits, is superior to chemical block, because regeneration can be more readily prevented and because postganglionic degeneration, with its undesirable phenomena, need not be produced.

Of 62 patients treated by White¹¹⁵ with paravertebral injections of alcohol for angina pectoris, 52 per cent had complete or nearly complete relief from pain, while 30.5 per cent had reduction of severe attacks to a mild form, which could be treated satisfactorily by routine medication. An unsatisfactory result was obtained in 9.5 per cent, and 8 per cent died within two weeks of the injection. In the author's opinion, alcohol injections should be reserved exclusively for the patient with intolerable pain who is a poor operative risk. He describes the technic in detail.

Certainly no other method, such as total thyroidectomy, cardiomyopexy, omentopexy or cervicodorsal sympathectomy, can offer such results to the severely handicapped patient. Our method of choice for younger and not too severely handicapped patients is dorsal sympathectomy, but this operation cannot be carried out on the majority of patients. The complications of alcohol block, such as pleuritic pain, pneumothorax, intercostal neuritis and occasional coronary thrombosis, are offset by the spectacular relief from pain which occurs in half of the intractable cases.

115. White, J. C.: Technique and Paravertebral Alcohol Injection: Methods and Safeguard in Its Use in the Treatment of Angina Pectoris, Surg., Gynec. & Obst. **71**:334 (Sept.) 1940.

The prevention of ischemic gangrene following occlusion of the major peripheral arteries by paravertebral block is stressed by Gage and Ochsner.¹¹⁶ They employed the block of the sympathetic nerves as a preliminary procedure to the ligation of major arteries in 10 cases. In all but 2 cases the collateral circulation was found to be inadequate. In no case did gangrene set in after the main artery was tied. Acute arterial embolism was treated in the same manner in 4 additional cases. The authors state that sympathetic block successfully counteracts the perverted physiologic processes which occur when a major artery is occluded. It dilates the main and collateral vessels, raises the arterial and venous pressures, increases the flow of blood per minute through the main and collateral arteries and increases arteriolar pulsations and lymph flow. The size and number of the vasa vasorum are increased; collateral vessels develop more readily, and the blood supply of the muscles improves. All in all, it prevents ischemic gangrene. They favor repeated procaine block against permanent destruction of the sympathetic chain and ganglions.

Our experience with this method has been equally favorable. In the case of the handicapped patient who has just suffered acute arterial embolism after auricular fibrillation or mural thrombosis in the left side of the heart, the method is admirably suitable for the protection of the limb against gangrene. When deliberate ligation of major arteries is contemplated in a case of peripheral aneurysm, such as one of the iliofemoral or popliteal arteries, surgical sympathectomy, as advocated by Veal,¹¹⁷ has yielded us excellent functional results.

VENOUS OCCLUSIONS

Glasser and Lesser¹¹⁸ report 20 cases of severe organic arterial disease of the lower extremities in which arteriosclerosis was the predominant feature. Ligation of the femoral vein was performed in all cases. In 16 cases the relief of pain within twelve hours was dramatic. In 2 of 18 cases in which the pedal pulses were absent the pulses became palpable. In 10 of 17 cases in which gangrene was present definite demarcation, with spontaneous separation of the localized gangrene, was obtained. In 5 cases progressive spread of gangrene necessitated mid thigh amputation.

116. Gage, J. M., and Ochsner, A.: The Prevention of Ischemic Gangrene Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, *Ann. Surg.* **112**:938 (Nov.) 1940.

117. Veal, J. R.: The Value of Sympathetic Interruption Following Surgical Repair of Peripheral Aneurysms, *M. Ann. District of Columbia* **9**:227 (July) 1940.

118. Glasser, S. T., and Lesser, A.: Femoral Vein Ligation for Chronic Arterial Diseases, *Am. J. Surg.* **52**:100 (April) 1941.

In previous reviews we have reported on attempts to improve circulation by ligation of concomitant veins. There is good experimental and clinical evidence that when a major artery is ligated the concomitant vein is advantageously tied. But in the case of chronic vascular occlusion the procedure is fraught with the danger of accelerating gangrene or stirring up infection. As a prophylactic measure against pulmonary embolism, however, Veal¹¹⁹ has conclusively shown its value in amputations of the lower extremity.

In a thought-provoking article Homans¹²⁰ points to thrombosis of the deep veins of the lower leg as a source of pulmonary embolism. This type of thrombosis is difficult to identify, although lameness on walking up and down stairs, pain in the popliteal fossa on dorsiflexion of the foot, slight edema and cyanosis limited to the lower portion of the leg are highly suggestive. Conservative treatment is justified only until such signs and symptoms recur after immobilization. In the presence of a bland thrombus below the knee the common femoral vein is exposed, and if it is free of clots the superficial femoral vein may be tied. This will not lead to cyanosis or swelling of the leg. If a clot is found in the deep or the superficial femoral vein, it is sucked out, if possible, and the vein is tied or sutured. Heparinization of the patient follows. Ligation of the common femoral and the deep femoral vein produces permanent cyanosis and edema but may be a life-saving procedure. Sears¹²¹ has also reported some instructive cases of ligation of the femoral vein.

The crux of the situation is an early and accurate diagnosis of the bland, nonadherent thrombus at or below the knee. In an important monograph Bauer¹²² reports the results of venographic study of thromboembolic disease of the lower extremities. He believes that this process invariably starts in the deep veins of the lower portion of the leg. Its earlier stages can be unmasked by injecting contrast material into the short saphenous vein. If the deep veins of the lower part of the leg do not fill and yet the femoral vein is visualized, the foot of the bed is elevated and heparin is administered. If the femoral vein is also invisible, there are two possibilities. Tenderness over the femoral vein

119. Veal, J. R.: High Ligation of the Femoral Vein in Amputations of the Lower Extremities, *J. A. M. A.* **114**:1616 (April 27) 1940.

120. Homans, J.: Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, *New England J. Med.* **224**:179 (Jan. 30) 1941.

121. Sears, J. B.: Experience with Femoral Veins: Ligation for Prophylaxis of Postoperative Pulmonary Embolism, *New England J. Med.* **224**:108 (Jan. 16) 1941.

122. Bauer, G.: A Venographic Study of Thrombo-Embolic Problems, *Acta chir. Scandinav. (supp. 61)* **84**:1, 1941.

and swelling of the thigh are signs of an adherent thrombus. Heparin will be useful only in preventing propagation of this thrombus or in preventing thrombus formation in the veins of the muscles of the other leg. If there is no tenderness over the femoral vein and yet roentgenograms reveal no filling, the risk of pulmonary embolism is great, because there is a bland, nonadherent, floating thrombus in the femoral vein. Elevation of the limb and energetic treatment with heparin are indicated; ligation of the vein is done in case an infarct has occurred. To determine the site of ligation the long saphenous vein is exposed and through it the iliofemoral segment is visualized. If the femoral vein is free, it is ligated below the vena profunda; if the deep femoral or the iliac vein is involved, a ligature of the vein has to be made above the thrombus.

One can readily object to such a simplification of a complicated and unpredictable course of events, but important lessons, which are corroborated by clinical experience, can be learned from this study. One is the frequency with which typical iliofemoral thrombosis actually starts in the muscles of the calf. This treacherous, often unrecognized, thrombosis, to which Homans first drew attention, was discussed in last year's review. Another lesson is the necessity of stressing the well known clinical fact that once a typical milk leg appears in the form of painful, deep thrombophlebitis in the groin, the danger of pulmonary embolism is slight. The real danger comes from the unrecognized floating thrombus in the femoral vein which is not tender to pressure and produces no edema; the condition can probably be most accurately diagnosed by venographic examination. Dougherty and Homans¹²³ have described a simple procedure.

Veal¹²⁴ gives an excellent description of a syndrome based on personal experience with 17 cases of axillary or subclavian venous thrombosis. The chief symptoms are pain in the arm and shoulder; massive pitting edema of the entire extremity; weakness and partial loss of function of the arm; preservation of the radial pulse; elevation of the systolic arterial pressure on the affected side; palpable, tender, cordlike swelling along the course of the brachial basilic or axillary veins; marked elevation of the local venous pressure, and decrease in the oxygen content of the venous blood of the affected arm. He emphasizes the post-thrombotic syndrome, the severity of which depends on the adequate development of collateral circulation. He believes that surgical procedures for this syndrome are not justified.

123. Dougherty, J., and Homans, J.: Venography: A Clinical Study, *Surg., Gynec. & Obst.* **71**:697 (Dec.) 1940.

124. Veal, J. R.: Thrombosis of the Axillary and Subclavian Veins with a Note on the Post-Thrombotic Syndrome, *Am. J. M. Sc.* **200**:27 (July) 1940.

In our experience the early forms of the condition respond well to repeated procaine blocks of the stellate ganglion; in the late forms resection of the thrombosed venous segment, which serves as a focus of irritation for vasomotor reflexes, has been worth while.

ARTERIAL OCCLUSIONS

Pearse¹²⁵ reviews in detail the various methods used for gradual occlusion of large arteries. After many trials on dogs he found that cellophane wrapped loosely around large arteries, such as the thoracic aorta or the carotid arteries, had an irritant quality which caused a steadily progressive constriction of the vessel, and even obliteration in some instances. The constriction may become so tight that it results in rupture of the aorta. The only drawback of the method is the intensity of the reaction caused by the cellophane.

The clinical implications of such aseptic, gradual occlusions are obvious. Thus such arteries as the carotids or the aortic bifurcation, the sudden closure of which may be disastrous, could be gradually occluded by placing a graded amount of tissue irritant around them. No clinical report has become available so far, but the use of this procedure seems promising.

Murray and Janes¹²⁶ report an interesting set of experiments in preventing failure of circulation following injuries to large arteries. They inserted glass cannulas between the cut ends of the common carotid arteries of dogs and secured them by tying a linen ligature around the cut ends of the vessels and the cannulas. Without the use of heparin the tubes became plugged in twenty minutes, but heparin kept the cannulas patent by raising the clotting time to thirteen minutes and more.

Consideration of the experimental evidence suggests that it might be possible to insert a glass cannula into a torn artery soon after an accident. With suitable hourly injections of heparin the cannula could be kept patent until the injured person could be removed to a hospital for final repair of the vessel.

Smith¹²⁷ described a new technic for simplifying vascular anastomoses, in which a soluble rod made of dextrose and coated with an oily lubricant (such as a mixture of theobroma oil U. S. P. [cocoa butter] and paraffin) is introduced into the vessel. This mechanical form facilitates the proper approximation and suture of the ends of the

125. Pearse, H. E.: Experimental Studies in the Occlusion of Large Arteries, *Ann. Surg.* **112**:934 (Nov.) 1940.

126. Murray, G., and Janes, J. M.: Prevention of Acute Failure of Circulation Following Injuries to Large Arteries: Experiments with Glass Cannulae Kept Patent by Administration of Heparin, *Brit. M. J.* **2**:6 (July 6) 1940.

127. Smith S.: A Soluble Rod as an Aid to Vascular Anastomosis: An Experimental Study, *Arch. Surg.* **41**:1004 (Oct.) 1940.

vessel, just as a wooden egg aids in the mending of a stocking. The soluble rod dissolves in the blood stream within a minute after the circulation is released.

Linton¹²⁸ emphasizes the great importance of thrombosis occurring distal to the embolic occlusion of major arteries. The most common cause of gangrene following peripheral embolism is failure to institute adequate treatment before the arteries distal to the embolus have been irreparably damaged. Marked peripheral vasoconstriction of the arteries distal to the site of occlusion uniformly occurs soon after the lodgment of the embolus. The artery proximal to the embolus is not affected to the same degree. The restoration of the circulation following peripheral embolism can be brought about by early adequate treatment, possibly within the first six hours. The place and value of embolectomy, intermittent venous congestion, paravertebral sympathetic block and heparin are discussed. The article is strongly recommended to all internists dealing with cardiovascular emergencies.

Peripheral arterial embolism as seen and treated at the Cook County Hospital, in Chicago, is discussed by Koucky, Beck and Hoffman,⁴⁹ who give a true picture not of the ideal procedure but of what is actually happening in large charity hospitals throughout the country, with the majority of physicians still not alert to the grave implications of acute vascular occlusion. They emphasize the proper time of amputation when embolectomy has failed or is deemed not indicated and warn of waiting too long when toxemia is evident. The use of heparin as a valuable adjunct in cases of arterial suture, arteriovenous fistula, venous grafts and arterial embolism is again discussed by Murray.¹²⁹ One hundred and twenty-five patients with thrombophlebitis, phlebothrombosis and pulmonary embolism were treated, with marked success. Of 46 patients with pulmonary embolism, only 2 had further small emboli, even though heparin has no effect on existing thrombi.

It seems to us that heparin is clearly indicated now after arterial or venous suture or in cases of pulmonary embolism. As a preventive measure its use seems justified only in the "endangered" group, that is, elderly patients who have had an attack of venous thrombosis or pulmonary infarct.

Crafoord and Jorpes¹³⁰ treated 325 patients with injections of heparin postoperatively. Not a single thromboembolic episode occurred. Of a control series of 1,111 patients with a similar condition, this

128. Linton, R. R.: Peripheral Arterial Embolism, *New England J. Med.* **224**: 189 (Jan. 30) 1941.

129. Murray, G.: Heparin in Thrombosis and Blood Vessel Surgery, *Surg., Gynec. & Obst.* **72**:340 (Feb., no. 2 A) 1941.

130. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, *J. A. M. A.* **116**:2831 (June 28) 1941.

complication occurred in 9 per cent. In both series the patients selected were over 35 years of age and had been subjected to operations on the gastrointestinal tract, the biliary system or the urinary passages or to major operations for hernia or varices. Heparin was given intermittently in intravenous injections four times a day. The treatment was continued for five to ten days.

We have tried both the continuous and the intermittent administration of heparin. Certainly the patient is far more comfortable if the continuous intravenous drip is avoided. Not enough is known, however, about the dangers of the marked fluctuations of coagulation time which follow single intravenous injections of heparin.

Repeated removal of emboli, caused in 1 case by a sarcoma dislodged from the pulmonary veins¹³¹ and in another by a fibrillating heart,¹³² brought about permanent restoration of circulation in seemingly hopeless cases. In both instances the embolectomies were aided by the use of heparin.

The mechanical and vasomotor effects of an arterial ligature are analyzed by Leriche and Werquin.¹³³ The ligature acts as a severe trauma and produces reflex vasoconstriction distally. This reflex may be removed by resection of the obliterated length of the affected artery. They prove with arteriograms that when the collateral way is clear and thrombosis is not too extensive the artery becomes filled with opaque substance below the occlusion. When healthy muscles are present near the ligated artery and run parallel to the obstructed vessel the anastomotic arteriolar circulation is of great value. Ligature is dangerous when the neighboring muscles have a divergent pattern and no vascular anastomoses exist between them. The prophylactic measures against gangrene, ischemic sclerosis, claudication and trophic disturbances following ligature of major arteries are listed as (1) the use of suture instead of ligature whenever possible, (2) limited resection of the artery between two ligatures, (3) periarterial sympathectomy above the ligature and (4) infiltration or section of the regional portion of the sympathetic trunk and ganglions.

The article is an excellent summary of Leriche's many years of investigation in this field. Traumatic and military surgeons will derive a great deal of information from its study.

Leriche⁴⁶ describes the syndrome of terminal aortic occlusion by arteritis, characterized by sexual impotence in the male, weakness and

131. Groth, K. E.: Tumor Embolism of the Common Femoral Artery Treated by Embolectomy and Heparin, *Surgery* 8:617 (Oct.) 1940.

132. MacFarlane, J. A.: Multiple Emboli Treated Surgically, *Brit. M. J.* 1:971 (June 15) 1940.

133. Leriche, R., and Werquin, M. G.: Effects of Surgery on the Vasomotor System, *Lancet* 2:296 (Sept. 7) 1940.

fatigue of the lower extremities, muscular atrophy and pallor of both limbs. There are no pulsations in either groin, but there is increased pressure in the upper extremities. As the condition advances the legs become cyanotic and desquamation of the skin develops, with small ulcerations. In 5 cases the first lumbar sympathetic ganglion was removed bilaterally; in 1 case resection of the thrombosed segment of the aorta and the iliac arteries was done in addition to sympathectomy. This seemed more beneficial than sympathectomy alone.

It is difficult to evaluate this procedure as the period of follow-up is short and the clinical data are meager. As usual, Leriche has a stimulating idea, which others might place on a more sound basis.

ANEURYSMS

In a symposium of the American Surgical Association the surgical treatment of aneurysm of the abdominal aorta was discussed by Matas, Bigger and Elkin. Matas¹³⁴ described the successful cure of an aneurysm of the abdominal aorta which he brought about in 1923. The patient died of tuberculosis more than one year after the operation. At autopsy it was demonstrated that collateral circulation above and below the aneurysm was well established. The clinical evidence of cure was confirmed by complete consolidation of the contents of the sac. The cotton tape ligatures employed in this case were well tolerated by the tissues. They caused a total aortic occlusion for the first nine days after the operation, after which they yielded slightly. Nevertheless, the sac filled with a clot because of the marked reduction of the aortic stream.

Bigger¹³⁵ collected the cases of ligation of the abdominal aorta previously reported in the literature and added 2 others. In the first case, the patient was a poor surgical risk; cardiac failure developed, and death followed occlusion of the aorta proximal to the aneurysm. In the second case, the patient was a young man whose ruptured traumatic aneurysm was treated by preliminary occlusion of the aorta proximal to the sac. A month later a restorative endoaneurysmorrhaphy was done. A year after this operation the patient appeared to be well; there was no evidence of the aneurysm, and the lumen of the aorta was obviously patent.

Elkin,¹³⁶ after reviewing the literature, reports the proximal ligation of a large pulsating aneurysm situated just below the origin of the inferior mesenteric artery. Two cotton tapes were tied around the aorta

134. Matas, R.: Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common Iliac Arteries, *Ann. Surg.* **112**:909 (Nov.) 1940.

135. Bigger, J. A.: The Surgical Treatment of Aneurysm of the Abdominal Aorta, *Ann. Surg.* **112**:879 (Nov.) 1940.

136. Elkin, D. C.: Aneurysm of the Abdominal Aorta, *Ann. Surg.* **112**:895 (Nov.) 1940.

until the pulsation of the femoral vessels could hardly be felt. Since there was no increased vascularity about the aneurysm, it was thought best to produce a partial occlusion. Eleven months later there was a slight pulsation in the mass. The patient had resumed his ministerial duties and was driving his car.

Elkin discusses certain inherent difficulties in ligation of the aorta, aside from the technical performance. First of all, the location of the aneurysm is rarely at a point where proximal ligation can be undertaken without menace to the vitality of the kidneys or intestine. The most frequent site is in the region of the celiac axis, and partial distal ligation, which is not an especially successful procedure, is the only possibility. Only rarely is an unruptured aneurysm found at the iliac bifurcation and in such a position that the aorta can be occluded distal to the inferior mesenteric artery. Complete ligation above that vessel would very likely result in gangrene of the sigmoid flexure of the colon.

An efficient collateral circulation rarely exists about an aortic aneurysm, and gangrene of the extremities will result if the vessel is occluded. But if the collateral circulation is efficient, vessels may reenter the aneurysmal sac and cause an early recurrence.

The type of ligature and the manner of occlusion still remain an unsolved problem. Possibly the method of Pearse, with the cellophane reenforced by partial tape ligatures or sclerosing solutions between partial ligatures, may offer a solution.

The effect of aortic ligation on the heart has been a subject of much dispute and is still unsettled. Failure of the left side of the heart occurred in some patients soon after ligation.

It seems to us that with an earlier diagnosis and the use of the principle of gradual occlusion an occasional patient might be restored to economic efficiency. This has certainly been true of patients with wired aneurysms of the thoracic aorta.

Holman¹³⁷ reviews a group of 21 cases of arteriovenous fistula and adds interesting experimental observations which tend to show that after the establishment of a large arteriovenous fistula the heart first diminishes in size and then gradually dilates. The dilatation is not restricted to the heart but affects all the vessels involved in the fistulous circuit. When dilatation of the heart outstrips hypertrophy, decompensation occurs; when dilatation is paralleled by a commensurate hypertrophy, great enlargement and dilatation of the heart may occur without decompensation. The physiologic effect of the fistula depends on the volume of blood diverted through the fistula and therefore on its size.

The transient high systolic and diastolic pressures that persist for several days after operative closure of the fistula are due to the increase

137. Holman, E.: Clinical and Experimental Observations on Arteriovenous Fistulae, *Ann. Surg.* **112**:840 (Nov.) 1940.

in blood volume that has occurred during the existence of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased peripheral resistance.

The author shows on the basis of detailed case reports that complete cardiac decompensation, with peripheral edema, ascites, hydrothorax and extreme dilatation of the heart, may be corrected, with return of the heart to its normal size after closure of the fistula. An increase in blood pressure and a fall in pulse rate occurring on digital closure of the fistula indicate that the fistula is large, that it will not close spontaneously and that it will almost certainly produce deleterious effects on the circulation. The increase in blood pressure and fall in pulse rate are the first evidence that the circulatory bed is beginning to dilate, even though such dilatation may not be detectable by the usual means. The extent of the increase in blood pressure and fall in pulse rate depends on the duration of the fistula. It is greatest in the fistulas of long duration, with great cardiac dilatation.

A temporary but great increase in blood pressure and fall in pulse rate may occur immediately after the surgical closure of the fistula. These changes are due to a great increase in blood volume, which is an inevitable accompaniment of a large fistula of long duration. The increased blood volume is reduced immediately after the operation, but transient overdilatation of an already dilated heart may occur because of the redistribution of the formerly diverted blood into its normal channels.

Whether the increased blood volume is responsible for the cardiac dilatation or whether, as Reid¹³⁸ has suggested, the increase in blood volume is connected with the impending cardiac failure is a debated question. It is certain that we have repeatedly amazed our medical colleagues by demonstrating to them the rapid decrease of the size of the heart to normal following the operative closure of a fistula.

Lee and Freeman¹³⁹ reported 3 cases in which angioma of the lower extremity was fed from the venous side through back pressure on standing instead of from the arterial side, as in the more common type of congenital arteriovenous aneurysm. That filling occurred from the venous side was proved by lack of pulsation of the veins, absence of increase in the oxygen saturation of the venous blood taken from the affected extremities and prevention of filling by the application of a venous tourniquet.

The treatment suggested is a ligation of the veins with incompetent valves, with subsequent sclerosis of the remaining segment if necessary.

138. Reid, M. R., in discussion on Holman.¹³⁷

139. Lee, W. E., and Freeman, N. E.: Circulatory Disturbances Produced by Extensive Angiomata of the Lower Extremities Associated with Varicose Veins, *Ann. Surg.* **112**:960 (Nov.) 1940.

In the cases reported the ligation of the incompetent veins not only reduced the size of the angioma but relieved the marked postural hypotension, which was severe enough to cause fainting. In 1 patient the increase in volume of the lower portion of the leg when the erect posture was assumed was 475 cc.

This postural hypotension due to defective venous valves and consecutive "bleeding" into the affected extremity is not infrequent in cases of extensive varicose veins. In cases of congenital venous aneurysm the capacity of the venous bed is even greater. The syndrome should be emphasized, as it may be confused with the carotid sinus syndrome.

Cases of arteriovenous fistula of the limb are described by Lewis¹⁴⁰ in which the circulation of the distal part of the limb becomes restored to, or actually beyond, normal over a period of years. Such restoration may be due in part to decreased vasomotor tone, but may result also from vascular growth. The latter may be controlled by a chemical stimulant arising locally as a product of the need of the tissues and acting locally.

This report touches on an important surgical problem. The surgeon usually likes to wait six months or longer after the development of an arteriovenous fistula before he attempts repair. On the other hand, a large fistula throws such a burden on the heart that waiting too long may bring about irreversible damage. The suggestion of Gage and Ochsner and Veal to increase collateral circulation in the affected limb by a preliminary sympathectomy is germane to this discussion. While Lewis' presentation, as always, is concise, simple and logical, his hypothesis is not supported by observations on simple arterial aneurysm, associated with which there is often great need for blood and vascular growth and in which collateral circulation is notoriously poor. The diversion of blood into the venous channels, the high oxygen saturation of the venous capillary blood and its more facile diffusion into the tissues must be responsible for the more rapid growth of vascular tissue in arteriovenous fistulas; as a matter of fact, bone grows faster and the entire limb gets larger in patients whose epiphyses are not yet closed.

THE CAROTID SINUS SYNDROME

Mulholland and Rovenstine¹⁴¹ review the diagnosis, surgical procedure and preoperative and postoperative care in 5 cases of carotid sinus syndrome. In all 5 cases diagnosis was made by digital pressure over

140. Lewis, T.: The Adjustment of Blood Flow to the Affected Limb in Arteriovenous Fistula, *Clin. Sc.* 4:277 (Oct.) 1940.

141. Mulholland, J. H., and Rovenstine, E. A.: Surgery in the Carotid Sinus Syndrome, *Surgery* 9:751 (May) 1941.

the bifurcation of the common carotid artery at the level of the upper border of the thyroid cartilage. The pulse rate, blood pressure and electrocardiographic changes were determined during the manipulation. The patients were classified into vagal, pressor and cerebral types. When the carotid sinus nerve was blocked with procaine, pressure over the carotid bulb should have given no symptoms.

It is striking that the patients were all about or over 60 years of age and might have had disturbances of the cerebral or cardiac circulation. It may well be that the exaggerated reflex phenomena were not due to an increasingly sensitive carotid sinus, but that the cerebral reflex arc or the end organs in the cardiac muscle were hyperreactive. When this is the case the sensitive carotid sinus plays a minor part in the disturbed reflex. Further studies on this interesting surgical problem are indicated.

CERVICAL RIB AND THE SCALENUS SYNDROME

Jelsma ¹⁴² considers the history and symptoms of the scalenus syndrome; of 45 patients operated on, 26 had complete relief of pain one month after operation and 7 received satisfactory, but not complete, relief. Two obtained 50 per cent relief. The operations consisted of section of the muscles or neurolysis or both.

Kaplan ¹⁴³ analyzed the relation of the scalenus anticus muscle to pain in the shoulder. He emphasized the diagnostic significance of infiltrating the lateral margin of the muscle with solution of procaine hydrochloride to determine the influence of relaxing this muscle on the symptoms accompanying painful lesions of the shoulder. Among the conditions studied were the scalenus syndrome (16 cases, in 6 of which the condition followed trauma), subacromial bursitis with adhesions (12 cases) and lesions of miscellaneous origin (3 cases). The author believes that such lesions produce a secondary spasm of the scalenus muscle.

This analysis is timely, as it points to the importance of making an accurate diagnosis of the scalenus syndrome before section of the muscle is undertaken. While the operation is remarkably successful in the properly selected case, many patients undergo unnecessary operations without relief. In our experience subacromial bursitis, osteoarthritis of the cervical portion of the spine and early degenerative lesions of the spinal cord must be carefully eliminated before scalenotomy is advised. Kaplan reports striking results from repeated injections of procaine hydrochloride into the muscle.

142. Jelsma, F.: Scalenus Anticus Syndrome: End Results of One Hundred and Fifteen Cases, *Internat. Clin.* **4**:219 (Dec.) 1940.

143. Kaplan, C.: Relation of the Scalenus Anticus Muscle to Pain in the Shoulder, *Arch. Surg.* **42**:739 (April) 1941.

SYMPATHECTOMY IN TREATMENT OF PERIPHERAL CIRCULATORY
DISTURBANCES

In spite of many hundreds of operations on the sympathetic nervous system, surgeons had to base their scheme of the outflow of preganglionic fibers from the cord to the limbs on the early experiments of Langley, Bayliss and Bradford, who used erection of hairs, sweating or vascular changes for recording sympathetic activity. Furthermore, the experiments were carried out on cats and dogs, which possess thirteen thoracic and seven lumbar spinal nerves. Sheehan and Marrazzi¹⁴⁴ utilized rhesus monkeys because they possess twelve thoracic nerves, as does man. Thus, whereas seven spinal roots participated in the preganglionic outflow to the lower extremity of the cat, only four roots contributed in the monkey—the twelfth thoracic to the third lumbar root, inclusive. In the upper limb of monkeys the outflow of preganglionic sympathetic fibers was confined to from the fourth to the eighth thoracic root, inclusive, with the major outflow occurring from the fifth, sixth and seventh thoracic spinal nerve roots.

Experiments on monkeys designed to study pathways of the sympathetic nervous system are gaining in importance; much previous knowledge, based on experiments with cats and dogs, will have to be revised.

During the past five years, Smithwick¹⁴⁵ has done 115 preganglionic sympathectomies for the upper extremity in cases of vascular spasm. He found that the upper extremity can be thoroughly sympathectomized by interrupting the outflow from the second and third dorsal segments and dividing the sympathetic trunk below the third dorsal ganglion. The outflow from the first dorsal segment is thus left intact. While the immediate results were satisfactory, the late results were variable, due mostly to regeneration of sympathetic motor fibers. A number of variations in surgical technic were tried to check regeneration. Finally, the anterior roots of the second and third dorsal spinal nerves were sectioned intraspinally, which leaves them in a water-tight compartment when the meninges heal. To prevent regeneration toward the decentralized second and third ganglions, these were wrapped in a small silk cylinder and the distal end of the trunk was ligated. Early results with this method have been excellent. Late results cannot yet be reported.

Smithwick feels that the immediate and early results of preganglionic denervation of the upper extremity are uniformly satisfactory. Here

144. Sheehan, D., and Marrazzi, A. S., Jr.: Preganglionic Outflow to the Limbs of Monkeys, *J. Neurophysiol.* **4**:68 (Jan.) 1941.

145. Smithwick, R. H.: The Problem of Producing Complete and Lasting Denervation of the Upper Extremity by Preganglionic Section, *Ann. Surg.* **112**: 1085 (Dec.) 1940.

the degree of damage to tissue or local fault in the vessel wall is the limiting factor. If late results are not as satisfactory, this is due in the great majority of instances to regeneration. Therefore, the present surgical trend is to avoid or minimize this regeneration. He points out, however, that even if regeneration does take place, the patients are benefited by the operation. Their symptoms are milder and easier to control. The blood flow is well maintained from the shoulder to the mid-dorsum of the hand. The basal and middle portions of the fingers show an elevated temperature. The most marked change is in the finger tips. Regeneration is rarely complete, and the result is worth while from the patient's point of view.

Perhaps the best proof of Smithwick's contention that proper technic is of paramount importance in preventing regeneration is seen in the study of patients in whom one extremity remains dry, warm and free of spasm, whereas the other may show a small strip of moisture, cooling of the tips and recurrence of biphasic color changes. Yet both extremities have been denervated by the same technic in our clinics. One must assume with Smithwick that wide variations exist in the origin of pre-ganglionic pathways; certainly, the disease is the same in the two extremities, and the recurrence is not due to failure of sympathectomy to influence vasospastic vascular disease.

After studying 22 patients exhibiting Raynaud's phenomena, Johnson⁶⁹ concurs with Hutchinson's conclusion that Raynaud's disease is not a clinical entity and that the peripheral manifestations observed are merely symptoms of some more fundamental disease. This is also in accord with the views of Hunt, which were discussed in our review of 1937. Hunt expressed the belief that Raynaud's disease is rare and that the Raynaud phenomenon occurs in a wide variety of definite and indefinite disorders. Patients who exhibit Raynaud's phenomena but who have a well recognizable cause for it should obviously be treated for the underlying condition. Johnson's attitude toward sympathectomy for Raynaud's disease is that the operation has been a complete failure and that circulation returns to the preoperative level in a short time, together with the symptoms. He presents 5 case reports in support of this statement. He feels that in all cases the patient's circulation returned to the preoperative level, because (1) the finger plethysmograph, while showing increased pulse waves shortly after sympathectomy, showed tracings similar to the preoperative ones, (2) local application of heat produced approximately the same amount of vasodilatation before as after sympathectomy, (3) median nerve block showed varying and not readily explainable responses in the anesthetized and unanesthetized fingers and (4) the symptoms recurred rather early in most cases.

These statements are so challenging and are based on such a thorough and painstaking study that their critical analysis is worth

while. In the first place, the value of the finger plethysmograph as an instrument of measuring blood flow to the finger may be seriously questioned. The plethysmograph, as has been repeatedly pointed out, measures the amplitude of the pulse volume; it registers the rapid systolic forward flow, but not the smaller systolic back flow or the slow forward diastolic flow. The net arterial inflow depends not only on the first and third phase but on the amount of the second phase, which has to be subtracted. Nor does the plethysmograph measure the circulation time through the extremity, which is decreased after sympathectomy. Obviously, when blood flow is more rapid more blood can pass through a given part. When the rate of blood flow was studied it was found to range from 0.02 cc. per minute per 10 cc. of tissue when the vessels were constricted to 12 cc. when they were dilated as much as a hundred times; certainly the plethysmograph is not an accurate means of measuring the state of circulation through the fingers.

That local application of heat produces vasodilatation after sympathectomy is well known; the capacity of smooth muscle to relax on direct application of heat is maintained. If the author had studied the effect of indirect reflex heat on sympathectomized fingers he would have found, provided the sympathectomy was complete, that the reflex heat does not produce vasodilatation in sympathectomized fingers. This was demonstrated first by Lewis. The observations on the effect of median nerve block are confusing. In 1 case the nerve block resulted in increased oscillations before, but not after, sympathectomy. In another case the median nerve block produced marked increase in pulsations after sympathectomy in the three fingers innervated by the median nerve, in spite of absence of sweating. One patient became emotionally unstable; I felt faint. Certainly a median nerve block which fails to produce increased oscillations in the fingers either means severe organic damage or partial paralysis with stimulation of the vasoconstrictors. The phenomenon of cooling and diminished pulsations in the nonanesthetized fingers occurring in the author's cases after median nerve block can be explained by the painful stimulus of the injection, which produces vasoconstriction in the nonanesthetized fingers, but is unable to act on the fingers in which the vasoconstrictor fibers are blocked by procaine hydrochloride. On the basis of these findings, Johnson promulgates the startling hypothesis that Raynaud's phenomena are brought about by diversion of blood from the fifth finger and are not due to active vasoconstriction. Nothing but his misinterpreted findings supports his assumption.

Study of the cases of the surgically treated patients reveals that 2 patients were operated on when indications were doubtful: 1 for rheumatoid arthritis and 1 for syphilitic endarteritis. If these 2 patients

did not show clinical improvement the fault may lie in their selection. One patient had hysterical attacks, which sometimes lasted an hour, and the symptoms recurred eight days after operation. In 1 patient with bilateral removal of the stellate and third dorsal ganglion—the second is not mentioned—median nerve block released a vasospasm, which is a definite proof of regeneration of fibers or an incomplete operation. In another patient after both lumbar sympathectomy and bilateral preganglionic dorsal sympathectomy the sweating function in the arms and hands had returned in about six days. The fifth patient had a postganglionic sympathectomy on one side and a preganglionic sympathectomy on the other. The effects of direct heat and median nerve block were the same before and after the operation; no mention was made of the clinical result.

On the basis of these 5 cases in which surgical procedures were done the author concludes that surgical treatment of the sympathetic nervous system is a therapeutic failure. It should be pointed out that some of these operations were incomplete, as either sweating or vasodilatation to nerve block was demonstrated. In a case of preganglionic sympathectomy the vasomotor paralysis was so transitory that it did not last longer than the traumatic effects of the operation. The procedure used could hardly have been the one which White and Smithwick have gradually developed.

The difference of opinion expressed by these two articles by Smithwick and Johnson is not as great as it would seem. That secondary types of vasospasm simulating Raynaud's disease should be analyzed and treated on an etiologic basis requires repeated emphasis. Suitable methods of analysis undertaken on patients suffering from Raynaud's disease and subjected to adequate preganglionic procedures, which show absence of sweating and no or small rises of temperature after somatic nerve block, yield information which is contrary to Johnson's pessimistic view of the value of surgical treatment of the sympathetic nerves in cases of vasospastic disease. These methods have been reviewed in previous years. Johnson's report will undoubtedly stimulate the publication of carefully followed surgical cases.

The post-traumatic circulatory and trophic disturbances, which are receiving increasing attention in industrial surgery and in treatment of war wounds, are represented by two excellent articles. Herrmann and Caldwell¹⁴⁶ believe that such disturbances should be recognized early. In the acute phase periarterial sympathectomy brings about a quick response and the undesirable sequelae are prevented. When the acute phase is missed the circulatory and trophic changes run their

146. Herrmann, L. G., and Caldwell, J. A.: Diagnosis and Treatment of Post-Traumatic Osteoporosis, *Am. J. Surg.* **51**:630 (March) 1941.

own slow, and sometimes irreversible, course. In the discussion of this paper Herrmann does not recommend ganglionectomy for this condition.

Homans¹⁴⁷ described interesting cases of minor causalgia following injuries and wounds. He considers sympathetic block is the treatment of choice but states that periarterial sympathectomy or ganglionectomy may have to be done in cases of the severe form. There is little hysterical element in this disease; yet most cases are first regarded and handled as instances of hysteria.

SURGICAL TREATMENT OF HYPERTENSION

There is continued interest in the surgical treatment of hypertension, because rest, sedatives, toxic depressants and psychoanalytic sessions, while of unquestionable temporary, palliative value, have failed to cure or arrest the progress of this disease. Hypertension with its sequelae is responsible for more than half a million deaths annually in the United States.

Peet, Woods and Braden¹⁴⁸ report on 350 patients who have had bilateral supradiaphragmatic splanchnic nerve sections and lower dorsal ganglionectomies. The authors prefer to operate only on patients less than 50 years of age with a systolic blood pressure over 200 mm. of mercury, an ability to concentrate the urine to a minimum specific gravity of 1.021 and a nonprotein nitrogen level of less than 45 mg. per hundred cubic centimeters of blood. In the analysis of results, 86.6 per cent of the patients had postoperative relief of major symptoms, especially headache; 81.3 per cent had improvement or complete relief from incapacitation; 51.4 per cent had a significant reduction of blood pressure, and 11.7 per cent had a return of blood pressure to normal. Improvement in retinal findings was conspicuous in that papilledema disappeared in 73.8 per cent of patients and exhibited some improvement in 69.4 per cent. Cardiac improvement was manifested by a better electrocardiographic tracing in 53.4 per cent and diminution of the size of the heart in 64 per cent. The urea clearance improved in 52.2 per cent of the patients and the urine concentration in 44.8 per cent. In addition, the statement was made that the prognosis was better for women than for men, that the most favorable results were obtained in the age group below 30 and that the surgical mortality was

147. Homans, J.: Minor Causalgia Following Injuries and Wounds, *Ann. Surg.* **113**:932 (June) 1941.

148. Peet, M. M.; Woods, W. W., and Braden, S.: Surgical Treatment of Hypertension: Results in Three Hundred and Fifty Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathetic Ganglionectomy, *J. A. M. A.* **115**:1875 (Nov. 30) 1940.

3.4 per cent. The authors feel that their method offers the most hopeful approach among all surgical procedures.

It is interesting that in another larger series, that of Allen and Adson,¹⁴⁹ who report on 224 patients, the incidence of symptomatic relief and of lowering of blood pressure is approximately the same as that in the series just cited, although they employ a subdiaphragmatic splanchnic nerve section with partial resection of the celiac ganglion and also resect the upper two lumbar sympathetic ganglions. They state that while sympathectomy to produce permanent reduction of blood pressure is somewhat disappointing, the relief or amelioration of symptoms, with the extension of the expectancy of life for the patients in the advanced group, justifies the surgical procedure. In contradistinction to Peet and his co-workers, Allen and Adson feel that the results of operation for essential hypertension can be predicted with reasonable certainty by observing the response of the blood pressure to rest and sleep, to the ingestion of sodium amytal and to the intravenous injection of pentothal sodium. When poor results are predicted as a result of these responses the outcome is almost uniformly unfavorable. When good results are predicted some patients do not receive as much benefit from the operation as is anticipated.

Reports on a number of smaller series give essentially the same results as those of two large series just reviewed.¹⁵⁰ A courageous attempt to establish the value of and define the indications for surgical therapy is that of Rytand and Holman.¹⁵¹ Using the supradiaphragmatic approach, they operated on 40 patients of all ages, with congestive heart failure, outright coronary occlusion, hemiplegia and glomerulonephritis. The patients who had the most severe renal and retinal lesions fared worst; those with minimal or no renal or retinal lesions fared best. Of their series of 40 patients, only 6 could be seriously considered as having had their prognoses altered by the operation. Six more patients felt better, but their arterial pressures were not lowered. In 9 patients there was no change. Eleven died within one and one-half years, with their conditions unchanged; 8 died within two weeks of the operation, a surgical mortality of 20 per cent.

This article focuses interest on two factors which influence results of the surgical treatment. One is the grouping and selection of patients

149. Allen, E. V., and Adson, A. W.: Medical Versus Surgical Treatment of Hypertension, *Ann. Int. Med.* **14**:288 (Aug.) 1940.

150. Crane, W.: The Surgical Treatment of Essential Hypertension, *West. J. Surg.* **49**:88 (Feb.) 1941. Wertheimer, P.: La splanchnicectomie bilatérale sus-diaphragmatique dans le traitement chirurgical de l'hypertension artérielle, *Presse méd.* **48**:689 (Sept. 4-7) 1940.

151. Rytand, D. A., and Holman, E.: Arterial Hypertension and Section of the Splanchnic Nerves, *Arch. Int. Med.* **67**:1 (Jan.) 1941.

for operation. The four groups of Wagener, Keith and Barker, who classified diffuse arteriolar disease into early, moderate, marked and malignant forms, have been of great importance in predicting results. Not only is such grading applied to the patients in the Mayo Clinic, but the patients of Smithwick and those recently reported by one of us (G. de T.) and two associates were also subjected to it.¹⁵² The results to be expected are distinctly dependent on the stage of the disease in which the operation is undertaken. In fact, in a recent admirable statistical survey, Woods¹⁵³ has shown on the material of Peet and co-workers that life expectancy in the four groups is definitely prolonged after operation, as compared with the duration of life in the group reported by Wagener, Keith and Barker, in which no operation was performed. The importance of Keith's work, which originally met with so much opposition, is now becoming obvious to such surgical groups as originally had little use for it.

The surgical technic, as well as the stage of the disease, has an important bearing on results. Smithwick¹⁵⁴ describes an extended splanchnic nerve section which combines the advantages and eliminates the disadvantages of the two previous operations. It is a complete resection of the major splanchnic nerve, from the fifth dorsal root down to the celiac ganglion. In addition, the sympathetic ganglionated trunk is removed from the ninth dorsal ganglion to below the first, or occasionally the second, lumbar sympathetic ganglion. In order to obtain this exposure the diaphragm must be incised and resutured. The renal arteries, renal pelves, ureters and adrenal glands may be inspected and palpated. Smithwick, in a preliminary report, discussed patients operated on by this method and pointed to the marked postural hypotension which must accompany this operation before the splanchnic denervation can be called complete. It is our belief, based on some of our previous experience with the partial splanchnic nerve sections above or below the diaphragm, that the technic of Smithwick will greatly improve the results of, and may even extend the indications for, operation. Most convincing proof is afforded by patients who have had a splanchnic nerve section done by one of the previous methods, with a return of blood pressure to a preoperative level, and who after undergoing a complete splanchnic resection show an excellent response. In our clinic the supradiaphragmatic and infradiaphragmatic nerve sections gave only

152. de Takáts, G.; Heyer, H., and Keeton, R. W.: The Surgical Approach to Hypertension, J. A. M. A., to be published.

153. Woods, W. W.: The Surgical Treatment of Hypertension, abstracted, *Ann. Surg.* **113**:1072 (June) 1941.

154. Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension, *Surgery* **7**:1 (Jan.) 1940.

temporary results, or none at all; since the technic of Smithwick has been adopted not only the patients with early and moderately advanced disease but those in group III, with retinal hemorrhages and detectable renal damage, have been improved. Whether the malignant phase is operable or not is still under debate.

A further extension of the surgical treatment to total sympathectomy has been reported by Grimson, Alving and Adams.¹⁵⁵ At present this operation seems unnecessarily radical. It may become the operation of choice if the Smithwick procedure will not maintain its efficiency in the five and ten year follow-up records. It is recognized by all surgeons interested in this field that, just as in evaluating results of operations for cancer, longer follow-up periods are necessary.

The marked symptomatic relief from headache, dizziness and palpitation in some patients who show no, or hardly any, reduction in the level of blood pressure has received a possible explanation through the work of Heinbecker.¹⁵⁶ He states that in over 70 per cent of surgically treated patients, symptomatic relief is obtained, which he explains on the basis of adrenal denervation. In animal experiments he was able to show that the pressor substance produced by the ischemic kidney sensitizes the vessels to epinephrine and that when the secretion of epinephrine is decreased this reaction is diminished. In addition, he makes the point that the role of the surgeon in the problem of hypertension is to determine whether and in what type of cases renal-adrenal denervation will effect a permanent drop in blood pressure and restore renal circulation to normal. Splanchnic nerve section on human beings showed a reduction of blood pressure to normal when nervous influences are initiating the train of events that lead to a permanent organic phase of the disease; the operation will not lower blood pressure appreciably once the renal ischemia is affected by mechanisms not under nerve control.

We must take exception to this last statement; for several years we have taken specimens of renal tissue for biopsy while performing sections of the splanchnic nerve and have found that patients who have marked structural damage following toxemia of pregnancy, eclampsia or rheumatic infection may still respond well to operation. It is true, however, that in this group the return of blood pressure to normal may take several months, indicating perhaps slowly progressive improvement in renal ischemia.

155. Grimson, K. S.; Alving, A. S., and Adams, W.: Experimental and Clinical Basis for Total Bilateral Paravertebral Sympathectomy in Essential Hypertension, read at the meeting of the Central Society for Clinical Research, Chicago, Nov. 2, 1940.

156. Heinbecker, P.: Role for Surgeons in Problems of Essential Hypertension in Relation to Splanchnic Section, *Ann. Surg.* **112**:1101 (Dec.) 1940.

Cure of malignant hypertension in a child following nephrectomy is reported by Kennedy, Barker and Walters.¹⁵⁷ In a child of 7 years the removal of one kidney, which as a result of obstruction and infection had become atrophic, resulted in a return of blood pressure to normal. Before the operation the condition of the retina was characteristic of acute angiospastic retinitis. Shortly after the operation the changes in the ocular fundi were such that the ophthalmologist could state with confidence that complete recovery was assured.

Because of reports like these, the preoperative studies of hypertensive patients, especially the juvenile ones, should include a routine intravenous pyelogram. While some structural involvement of the other kidney may exist, the relief from hypertension may help its restitution. Late return of blood pressures to abnormal levels have been reported, however, and much interest is focused on five and ten year follow-up observations.

The improvement of renal circulation by omental or muscle grafts to the kidney has been attempted by Bruger and Carter.¹⁵⁸ Through an anterior, transperitoneal approach, omentum is sutured into the posterior cut surface of the renal capsule; when muscle is used, the capsule is stripped and the quadratus lumborum and psoas muscles are sewn into its place. Six of 9 patients operated on were relieved of their symptoms for two to eleven months. Headaches and vertigo had been especially striking in 4 of them. No measurable improvement of renal function was observed in any of these patients.

A similar negative result of renal grafts has been reported by two of us¹⁵⁹ (G. de T. and G. W. S.). We believed that incisions into the cortex of the kidney might help to establish vascular connections. Since the publication of our results, however, 1 of the patients, suffering from malignant hypertension with marked papilledema, has survived a five year period and is now free of symptoms and has no papilledema. Three additional patients have since had muscle implants into the kidney, in addition to a splanchnic nerve section. Histologic and dye injection studies would indicate that at least tubular circulation can be improved by these grafts. The combination of splanchnic nerve section with slender muscle grafts deeply implanted into renal parenchyma is now reserved for patients with more advanced renal damage.

157. Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in a Child: Cure Following Nephrectomy, *Am. J. Dis. Child.* **61**:128 (Jan.) 1941.

158. Bruger, M., and Carter, R. F.: Nephro-omentopexy and Nephromyopexy in the Treatment of Arterial Disease, *Ann. Surg.* **113**:381 (March) 1941.

159. de Takáts, G., and Scupham, G. W.: Revascularization of the Ischemic Kidney, *Arch. Surg.* **41**:1394 (Dec.) 1940.

AMPUTATIONS

Atlas¹⁶⁰ discusses the management of arteriosclerotic gangrene. He decries the recently created impression that gangrene is amenable to various forms of "conservative" therapy. This cannot be so because of the basic pathologic changes in the disease which affect the toes through occlusion of the digital arteries. These are end arteries, and there is little chance for rapid development of an effective collateral circulation. Conservative treatment should be considered when (1) the gangrenous process is localized to a single toe, (2) the gangrenous process is well demarcated with no tendency to spread, (3) there is no constitutional evidence of toxic absorption and (4) there is no cellulitis, osteomyelitis or lymphangitis. Conservative treatment consists of a prophylactic dose of gas and tetanus bacillus antitoxin on admission. Complete rest in bed is enforced, the leg being kept on a level lower than that of the heart. A cradle without light bulbs is used to protect the foot, and the gangrenous toe is kept scrupulously clean and protected by sterile dressings saturated with azochloramid or a suspension of zinc peroxide in sterile distilled water. Whisky is used as a vasodilating drug, and 100 cc. of a 5 per cent solution of sodium chloride is given intravenously every other day. When a gangrenous part is detached from the foot passive vascular exercise is started.

The operation of choice is the circular amputation through the lower third of the thigh, with primary closure. In the event of cellulitis or lymphangitis, a simple guillotine section through the upper third of the leg with the stump left open is rapidly performed under anesthesia. The open stump is treated with zinc peroxide. Sulfanilamide, high voltage roentgen radiation for gas bacillus infection and small blood transfusions are used when indicated. Later, when the risk of infection has abated, necessary stump revisions or reamputation at a higher level may be done. The danger of an infected amputation stump is that of septic pulmonary emboli. Ligation of the femoral vein just distal to the entrance of the saphenous vein at the time of amputation has lowered the mortality rate (Veal).

In a series of 28 patients with arteriosclerotic and diabetic gangrene Bowers and Kennedy¹⁶¹ reported major amputations in 70 per cent, without a single death. The authors' patients were unselected, but close cooperation between internist and surgeon was maintained. The high mortality, in their opinion, is partially due to the fact that the patient is incorrectly prepared. No major amputation was done when the

160. Atlas, L. N.: Arteriosclerotic Gangrene: Major Clinical Problem, *Am. J. Surg.* **49**:467 (Sept.) 1940.

161. Bowers, W. F., and Kennedy, J. C.: Improved Management of Gangrene of the Foot, *Am. J. Surg.* **50**:573 (Dec.) 1940.

temperature of the patient was over 100 F. To lower the temperature and pulse in any case of gangrene of the foot in which major amputation is necessary, the patient is taken to the operating room and after general anesthesia is induced (cyclopropane by inhalation or pentothal sodium by intravenous injection) all necrotic tissue is removed by sharp dissection until a flat bleeding wound is produced. This débridement may include one or more digits and metatarsal bones and all overhanging soft tissues. The wound then is covered with a heavy layer of 40 per cent cod liver oil ointment, and a sterile dressing is applied. The temperature usually drops dramatically the next morning. Herein lies the danger, a tendency to allow time for self healing. This should not be done. The operative technic consists of a low thigh amputation, without use of a tourniquet to avoid a nonhealing stump or retractors, and severing of all tissues on the same level, since the blood supply goes superficially almost at right angles. Skin flaps are fashioned to avoid "dog ears" at each corner. The stump is closed tightly by means of interrupted silk sutures. A petrolatum strip is placed over the incision, and the stump is covered by a smooth, snug dressing (gauze roll, 5 yards [4.57 meters]). The stay in the hospital was reduced to sixteen days for the arteriosclerotic patients and twenty-five days for the diabetic patients who had been conservatively treated before amputation.

Samuels¹⁶² repudiates as erroneous the assumption that diabetic gangrene with associated infection of the foot presupposes the extension of the infection throughout the entire extremity, particularly in the lymphatic vessels. He points out that if the urine of a patient cannot be made sugar free preoperatively with large doses of insulin an undrained infection of the foot is indicated and further medical treatment is a waste of time. Cyclopropane anesthesia is used. No tourniquet is provided. The procedure involves a supracondylar circular incision, the formation of flaps being avoided. This site is chosen because infection is almost always confined to the foot and also because thigh muscles are conserved and good length to the femur is preserved. By this technic the popliteal artery is found without difficulty, the sciatic nerve is not injected and no attempt is made to undermine tissues. Fine silk sutures are used to approximate the muscles and fasciae, and fine silk or silkworm gut is used on the skin. The patient is allowed out of bed the following day and in a wheel chair the second day. The sutures are removed on the sixth or seventh day. Amputation 8 inches (20.3 cm.) below the knee is attempted rarely, and only in those cases in which there is an oscillographic curve of 1.0 or more at the ankle level. The objections to this

162. Samuels, S. S.: Leg Amputations in Diabetic Gangrene, *Ann. Surg.* **112**: 105 (July) 1940.

procedure are the increased trauma necessary in the complicated dissection and poor protection for the end of the stump.

The three reviewed articles show sane conservatism in trying to save an extremity until it is useless, becomes intractably painful or endangers life. The mortality statistics are improving from year to year. The report of Bowers and Kennedy is encouraging. They follow Zierold's suggestion of debriding the gangrenous extremity before doing a formal amputation. This method deserves further trial and may save many lives.

Gallie¹⁶³ summarized the experience of physicians in the Canadian army with amputations of the lower extremity as follows: Syme's amputation when well done is the best of all amputations. Amputation through the calf is suitable for men and women who have a good deal of leisure and who are not called on to stand for more than short periods. For men who are forced to earn their living on their feet the Gritti-Stokes amputation is better than either amputation below the knee or amputation through the middle of the thigh. Stumps of such amputations remained satisfactory for twenty years. Any amputation, with the exception of Syme's, is disabling and, in spite of the wonderful contributions made by the artificial limb maker, leaves a man seriously handicapped. It is unreasonable to expect him to compete on even terms in the general labor market. This difficulty can be minimized by training in some vocation in which loss of a leg is relatively unimportant.

The conclusions enumerated were based on experience with 2,448 amputations of the lower extremity, of which 746 were in the leg, 142 at the ankle and 1,468 above the knee.

In the discussion of Gallie's paper, Kirk,¹⁶⁴ of the United States Army, states that leg makers have not made suitable prostheses for the Syme amputation. He disagrees with Gallie in regard to amputations below the knee, which he thinks often give good side-bearing stumps. Instead of the Gritti-Stokes procedure, he favors a plastic supracondylar amputation.

The importance of closer cooperation between surgeons and artificial limb makers is obvious. The Council on Physical Therapy of the American Medical Association has created a committee which is issuing its recommendations in current numbers of *THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION*. This material will be reprinted in book form. Medical preparedness certainly requires a few simple directions along this line.

163. Gallie, W. E.: The Experience of the Canadian Army and Pensions Board with Amputations of the Lower Extremity, *Ann. Surg.* **113**:925 (June) 1941.

164. Kirk, N. T., in discussion on Gallie.¹⁶³

News and Comment

Association of Military Surgeons of the United States.—The annual meeting of the Association of Military Surgeons of the United States will be held Oct. 29 to Nov. 1, 1941, at the Brown Hotel, Louisville, Ky. All members of the medical profession are invited to attend as guests, particularly members of the medical defense committees.

War medicine and surgery have changed considerably since the previous emergency. Mechanization of armies and air bombardments have created new and difficult problems in traumatic surgery and methods of treatments of wounds and extreme abrasions. The session will conclude with a mass review of military medicine and an inspection of Fort Knox.

The preliminary program of professional sessions of the meeting follows:

Col. Harold D. Corbusier, Medical Reserve, United States Army: Presidential Address.

Rear Adm. Ross T. McIntire, Surgeon General of the United States Navy: "Policies and Activities of the Medical Department of the United States Navy in the Present National Emergency."

Dr. Warren F. Draper, Assistant to the Surgeon General, United States Public Health Service: "Present Policies and Activities of the United States Public Health Service."

Brig. Gen. Frank T. Hines, Administrator of Veterans' Affairs: "Progress of the Part the Veterans' Administration Is Playing in the National Defense Program."

Major Frank B. Wakeman, Medical Corps, United States Army, representing Major Gen. James C. Magee, Surgeon General, United States Army: "Present Policies and Activities of the Medical Department of the United States Army."

Col. Robert H. Duenner, Medical Corps, United States Army, Fort Knox, Ky.: "Medical Service of the Mechanized Forces."

Col. Paul E. Howe, Sanitary Corps, United States Army: "Nutritional Problems of the Army."

Col. Fred H. Albee, Medical Reserve, United States Army: "Treatment of Ununited Fractures of Importance to the Military Service."

Capt. Lucius W. Johnson, Medical Corps, United States Navy: "Medical Service at Remote Naval Bases."

Capt. William L. Mann Jr., Medical Corps, United States Navy: "Medical Arrangements for Combined Operations of Land Forces and Sea Forces" (with motion pictures).

Papers are scheduled from the following speakers, but the titles are not yet available:

Major Gen. C. R. Reynolds, United States Army Ret.

Brig. Gen. Leigh C. Fairbank, Assistant to the Surgeon General, United States Army.

Col. Irvin Abell, of Louisville, Ky.

Col. Leonard C. Rowntree, Medical Reserve, United States Army; Chief, Medical Division, Selective Service System, Washington, D. C.

Col. Raymond A. Kelser, Veterinary Corps, United States Army.

Lieut. Col. David N. W. Grant, Medical Corps, United States Army, Office of the Chief of the Air Corps.

Book Reviews

Vitamin K. By H. R. Butt, M.D., Instructor of Medicine, Mayo Foundation, University of Minnesota, and A. M. Snell, Professor of Medicine, Mayo Foundation, University of Minnesota. Price, \$3.50. Pp. x + 172, with 39 illustrations and 14 tables. Philadelphia: W. B. Saunders Company, 1941.

Vitamin K is one of those substances which from time to time appear in medicine suddenly, entering the field with a fine flourish and performing in such a spectacular fashion that for a time they come to occupy the center of the stage.

Vitamin K was found unobtrusively. The original papers describing its usefulness in the treatment of a scurvy-like disease of chicks were published between 1929 and 1934. As so often happens, several years lapsed before clinicians realized the possible implications for human beings of a deficiency disease in chicks characterized by easy bleeding and relievable by a fat-soluble vitamin occurring in hog liver, hemp seed and certain cereals and vegetables. But in 1938 three independent papers drew attention to the fact that what was termed vitamin K had definite usefulness in overcoming the bleeding tendency encountered in cases of obstructive jaundice. Subsequently there has sprouted up a voluminous literature on vitamin K and substances with like effects. As a result new methods for studying diseases of the blood have been developed, new therapeutic weapons have been forged and a new chapter in medical discovery has been opened.

The authors of this small volume have done justice to their subject. They write well and modestly. They give all possible credit to Henrik Dam and his co-workers for the original discoveries. They do not lay undue emphasis on the fact that in the Mayo Clinic vitamin K was used for clinical work as early as anywhere. They review intelligently some 350 papers, putting in its proper relation to the total present knowledge of vitamin K what each one of these papers has added. On the whole, they give the history of vitamin K as it should be given. It is a dramatic story, told tersely and pungently and properly illustrated, and shows what an amazing substance this vitamin really is.

The Medical Aspects of Boxing. By Ernst Jokl. Pp. 251, with 54 illustrations. Pretoria, Union of South Africa: J. L. Van Schaik, Ltd., 1941.

This is an extraordinary book, since the writer has assembled not only an immense amount of information on the pathologic aspects of pugilism but a most interesting collection of the curiosa of boxing. It is a mine of useful material for the neurosurgeon, the athletic director and the industrial surgeon. The historical allusions and the interesting illustrations add to the readableness of the book. Perhaps most important of all is the proof that boxing should not be allowed in the air force, since even mild blows on the head may impair the sensitiveness of reflexes necessary in military aviation.

A Diabetic Manual. By Elliott P. Joslin, M.D. Seventh edition. Price, \$2. Pp. 238, with 53 illustrations and 24 tables. Philadelphia: Lea and Febiger, 1941.

To Dr. Joslin diabetes has always been a challenge. It is mainly this spirit of combat with and triumph over the disease running through his book that differentiates it from other manuals for the diabetic patient, and surely the new recruit will be cheered by the snapshots of previous patients "before and after." Everything the diabetic person needs to know is there, even if the epigrammatic style is a little tiring to the reader who goes straight through the book. Unfortunately, through the country in general there are still many physicians too ignorant or too lazy to take advantage of the newer knowledge of diabetes and many patients too apathetic to cooperate.

BRONCHIOLITIS FIBROSA OBLITERANS

REPORT OF A CASE

JOHN S. LADUE, M.D.

NEW ORLEANS

The symptom complex of bronchiolitis fibrosa obliterans, although fairly well defined, is one which usually escapes clinical recognition. This disease results from organization of fibrinous exudate in the bronchioles in response to local injury.

The total number of cases reported is small, and only 1 has been discovered among the 42,038 autopsies performed by members of the pathology department at the University of Minnesota Medical School since 1899. In this case the patient was studied clinically at the Minneapolis General Hospital, and I followed closely the course of his disease. It is hoped that a review of this case and a résumé of the literature may help to direct the attention of physicians to this disease when they are dealing with conditions having similar symptomatology.

Bronchiolitis fibrosa obliterans was first described and recognized as a pathologic entity in 1901 by Lange,¹ who differentiated between it and other processes which produce an overgrowth of fibrous tissue in the lungs, such as indurating, interstitial and organizing pneumonias. He discussed the clinical and pathologic findings in 2 cases but was unable to throw any light on the etiologic background of the disease. A year later, Fraenkel² reported the case of a patient presenting severe respiratory distress following the inhalation of fumes of nitric acid. At autopsy the same fibrosing process described by Lange was noted. Fraenkel divided the clinical course of the disease into three stages: first, several days during which the patient exhibits severe dyspnea, cyanosis and cough, but no elevation in temperature; second, a variable interval during which all symptoms are diminished, although

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1. Lange, W.: Ueber eine eigentümliche Erkrankung der kleinen Bronchien und Bronchiolen (Bronchitis et Bronchiditis obliterans), *Deutsches Arch. f. klin. Med.* **70**:342, 1901.

2. Fraenkel, A.: Ueber Bronchiolitis fibrosa obliterans, nebst Bemerkungen über Lungenhyperämie und indurierende Pneumonia, *Deutsches Arch. f. klin. Med.* **73**:424, 1902.

the temperature rises slightly, and, third, a final period during which the symptoms are markedly accentuated and the patient expectorates bloody sputum. The physical signs remain more or less constant throughout the course of illness. Many coarse rales can be heard over both lung fields, and there is increasing emphysema, which lessens somewhat in the second stage but grows worse again before death.

According to Edens,³ bronchiolitis fibrosa obliterans developed in 3 patients after inhalation of fumes of nitric acid, of sulfuric acid and of strong ammonia, respectively. Two survived, despite stormy illnesses, but the third patient succumbed in twenty-six days, with a progression of illness entirely similar to that of Fraenkel's patient.

Jochmann and Moltrecht⁴ reported cases of the disease following attacks of measles and of pertussis; Hart⁵ found bronchiolitis and alveolar septal pneumonia complicating measles. Wegelin⁶ studied a child who had severe respiratory distress after swallowing a prune pit, became dyspneic and cyanotic, improved temporarily and then died on the fifty-sixth day. Müller⁷ discovered characteristic microscopic lesions in 2 elderly patients who had had subacute bronchiolitis. Pernice⁸ reported a case of chronic bronchitis terminating in severe bronchiolitis. Wagner⁹ discussed a case of the same complex in a patient who had been exposed to the vapors of trinitrotoluene and who died within three weeks.

In a clinical lecture, Fraenkel¹⁰ briefly discussed 4 additional cases. Of 2 patients who had been exposed to acid fumes, 1 recovered. For 2 other patients no etiologic history could be established. One of them died within twenty-four hours, but the other lived fourteen days, and the diagnosis was made ante mortem.

Galdi¹¹ reported the characteristic postmortem findings in a 24 year old etcher. Blumgart and MacMahon¹² studied 5 patients. In 2 instances

3. Edens: Ueber Bronchiolitis obliterans, *Deutsches Arch. f. klin. Med.* **85**: 598, 1906.

4. Jochmann, G., and Moltrecht: Ueber seltenere Erkrankungsformen der Bronchien nach Masern und Keuchhusten, *Beitr. z. path. Anat. u. z. allg. Path.* **36**: 340, 1904.

5. Hart, C.: Anatomische Untersuchungen über die bei Masern vorkommenden Lungenerkrankungen, *Deutsches Arch. f. klin. Med.* **79**: 108, 1904.

6. Wegelin, C.: Ueber Bronchitis obliterans nach Fremdkörperaspiration, *Beitr. z. path. Anat. u. z. allg. Path.* **43**: 438, 1908.

7. Müller, F.: Die Erkrankungen der Bronchien, *Deutsche Klin.* **4**: 223, 1907.

8. Pernice, cited by Wegelin.⁶

9. Wagner, J.: Bronchiolitis Obliterans Following the Inhalation of Acrid Fumes, *Am. J. M. Sc.* **154**: 511 (Oct.) 1917.

10. Fraenkel, A.: Ein weiterer Beitrag zur Lehre von der Bronchiolitis obliterans fibrosa acuta, *Berl. klin. Wchnschr.* **1**: 6, 1909.

11. Galdi, F.: Pneumonia desquamativa obliterans nebst Bemerkungen über die Histologie der Lungeninduration, *Deutsches Arch. f. klin. Med.* **75**: 239, 1903.

12. Blumgart, H., and MacMahon, H.: Bronchiolitis Fibrosa Obliterans: A Clinical and Pathological Study, *M. Clin. North America* **13**: 197 (July) 1929.

there was nothing in the history to indicate the cause of the disease, the onset apparently occurring with a "cold." A chronic cough developed in a third patient after an attack of scarlet fever. Death occurred on the eighty-fourth day of hospitalization. Another had had asthma for two years, with chronic cough and progressive exacerbation of dyspnea, orthopnea and cough during the last five months of life. The fifth patient suffered from increasing cough and respiratory difficulty for three years after an attack of influenza; his illness ended with two weeks of acute pulmonary distress. Hübschmann¹³ also noted the lesions after an episode of influenza and found the Pfeiffer bacillus.

Martin, Rutishauser and Sciclounoff¹⁴ wrote of a patient seen and studied frequently for two years who complained of dyspnea, orthopnea and cough and who was treated at a sanatorium for tuberculosis, although no organisms were ever found in the sputum. Two injections of iodized poppyseed oil apparently aggravated all the symptoms, and the patient died twenty-four days after the second injection. From both roentgen ray and clinical findings, miliary tuberculosis was suspected before death. Assmann¹⁵ also described 2 cases in which the diagnosis was miliary tuberculosis, based on both clinical and roentgenologic study.

Leifer and Winkler¹⁶ reported an instance in which the diagnosis of bronchiolitis fibrosa obliterans was made before death and discussed the differential clinical symptoms and the important laboratory findings.

Muntsch¹⁷ reported observations on bronchiolitis fibrosa obliterans in a series of men who had been poisoned by gas in 1917. Winternitz¹⁸ produced lesions characteristic of the disease in dogs exposed to chlorine, phosgene (carbonyl chloride), chloropicrin (trichloronitromethane) and

13. Hübschmann, P.: Ueber Inthienzaerkrankungen der Lunge und ihre Beziehungen zur Bronchiolitis obliterans, Beitr. z. path. Anat. u. z. allg. Path. **63**:202, 1918.

14. Martin, E.; Rutishauer, E., and Sciclounoff, F.: Etude d'un cas de bronchiolite oblitérante avec thésaurisation pulmonaire du lipiodol injecté, Rev. de la tuberc. **3**:552 (May) 1937.

15. Assmann, H.: Die klinische Röntgendiagnostik der inneren Erkrankungen, ed. 5, Leipzig, F. C. W. Vogel, 1934.

16. Leifer, P., and Winkler, W.: Zur Diagnose der Bronchiolitis obliterans, Wien. klin. Wchnschr. **51**:1331 (Dec. 16) 1938.

17. Muntsch, O.: Leitfaden der Pathologie und Therapie der Kampfstoffkrankungen, ed. 4, Leipzig, Georg Thieme, 1936.

18. Winternitz, M. C.: Collected Studies on the Physiology of War Gas Poisoning from the Department of Pathology and Bacteriology, Medical Science Section, Chemical Warfare Service, New Haven, Conn., Yale University Press, 1920.

mustard gas (dichloroethyl sulfide). Bronchiolitis fibrosa obliterans was the most prominent postmortem finding in animals which survived for several days. Heitzmann¹⁹ showed early bronchiolar lesions in animals that lived only five to nine hours after the inhalation of phosgene.

According to the literature, on the basis of the etiology cases of bronchiolitis fibrosa obliterans seem to fall roughly into three categories. In the first, the disease apparently follows inhalation of irritant and damaging substances (such as fumes of nitric or of sulfuric acid, poison gases or vapor of certain solvents) or ingestion of foreign bodies. In the second can be cited instances in which the condition complicates certain acute infectious diseases, such as measles, influenza or scarlet fever, or occurs in the course of chronic bronchitis or asthma. The third category includes all cases in which the history is inadequate and those which must be accepted as idiopathic because no etiologic agent can be discovered.

The pathologic lesions can be closely correlated with the clinical symptoms and explain clearly the progressive nature of the disease. According to all investigators, the gross lesions observed at necropsy so closely simulate those seen in cases of miliary tuberculosis that an extensive and detailed search is made for a Ghon tubercle and despite its absence a gross diagnosis of miliary tuberculosis is the usual first verdict.

The lungs are usually distended, and numerous miliary nodules are seen beneath the pleura and diffusely scattered throughout the lung parenchyma. These are 1 to 3 mm. in diameter; they are sharply and often angularly circumscribed, are grayish white, firm and often scratchy on section and are found in the location of the terminal bronchioles. When the nodules are examined with a hand lens they can be differentiated from typical miliary lesions in that they are irregular instead of round, contain in their centers the distorted lumen of the involved bronchiole and show fine white streaks radiating from their centers. These streaks represent a stellate invasion of the adjacent parenchyma by the newly formed connective tissue. There is usually a definite area of injection surrounding each nodule. The lack of evidence of miliary involvement of the other organs of the body is striking and should make a pathologist wary of a diagnosis of miliary tuberculosis.

Microscopically, the lesions are typical and are easily differentiated from any other pulmonary lesion. Characteristically, the nodule consists of a partly destroyed bronchiole, with its lumen partly or completely

19. Heitzmann, O.: Ueber Kampfgasvergiftungen: IV. Ergänzende Befunde zur pathologischen Anatomie der Phosgenvergiftung, *Ztschr. f. d. ges. exper. Med.* **13**:181, 1921.

obliterated by an overgrowth of young granulation tissue. There may be an irregular proliferation of fibrous tissue about the wall of the bronchiole. Frequently the lumen is filled with detritus, consisting of desquamated epithelium, polymorphonuclear leukocytes, fibrin and blood, invaded by granulation tissue. The muscularis and elastic tissue fibers of the wall may show widespread destruction, with penetration and replacement by strands of connective tissue which are continuous with the fibrotic scarring about the bronchiole. This fibroblastic overgrowth sometimes extends like a polyp into the lumen from one side, or it may cause a uniform occlusion from all sides.

The pathogenesis has been noted by many writers, since all stages of the process can usually be seen in the sections. It begins with mild catarrhal inflammation of the epithelium, similar to bronchiolitis, which may be followed by sloughing of the epithelial layer. Later the membrana basalis, the stratum elastica, the stratum muscularis and the surrounding connective tissue become edematous and infiltrated with leukocytes and fibrin. Sometimes the entire bronchiole becomes necrotic and in microscopic sections is represented by a ragged bronchiectatic cavity or a miliary abscess.

More frequently, however, the repair of the damaged bronchiole begins before the necrosis becomes so extensive. Portions of the denuded epithelium are regenerated, but elsewhere, in the more severely damaged areas, the defects are repaired by dense fibrinous exudate, which is gradually liquefied. The adjacent connective tissue thus stimulated slowly proliferates and replaces the fibrin, with the aid of newly formed capillaries, until complete organization occurs. Sometimes a bronchiolar lumen may become narrowed by adult connective tissue and relined by normal ciliated columnar epithelium, a fact which may explain why some patients recover.

The end results depend on the degree to which the bronchioles are occluded. If they are completely closed, the alveoli supplied by a given bronchiole become atelectatic and sometimes are involved in the overgrowth of connective tissue. First the septal walls are thickened, and finally the alveolar spaces are filled with newly organized fibrous tissue. In such instances, care must be taken to make sure that the primary process is really in the bronchioles and does not represent an organizing or interstitial pneumonia.

When the bronchiolar obliteration is not complete the course of events is entirely different. Since inspiration is an active process and expiration a passive one, air can enter the obstructed passages more easily than it can leave. Hence the alveoli become distended with air, and true alveolar emphysema results.

The clinical symptoms are in great part determined by the degree of involvement and the progress of the pathologic lesion. In cases of inhalation of irritant fumes, the damage is widespread and severe respiratory distress rapidly ensues. The patient is extremely dyspneic and cyanotic during the stage of inflammation, destruction and desquamation of the bronchiolar epithelium. At this time there is usually low grade fever and cough, with minimal expectoration of mucoid, and occasionally bloody, sputum. Numerous rales are heard throughout both lungs. With expectoration of the debris occluding the bronchioles, the symptoms subside and the patient appears greatly improved. Within six to twenty days dyspnea and cyanosis recur and become progressively worse (a change corresponding to final obliteration of the bronchioles) until the patient dies. During the last two stages, rales may be heard at all times and are usually described as coarse but occasionally as crepitant. Signs of consolidation are lacking, and the temperature may be slightly elevated.

In other cases, as in that reported here, the damage spreads slowly, involving one part of the lung after another, with a corresponding increase in dyspnea and cyanosis and progressive weakness and loss of weight. Rales are heard rather late but become widespread before death. Cough with or without expectoration is a constant feature, and the temperature may or may not be slightly elevated.

REPORT OF CASE

A 20 year old Negro entered the Minneapolis General Hospital on Sept. 13, 1937 unconscious, dyspneic and cyanotic. Soon after admission he regained his senses. He stated that he had always been well until early that summer, when increasing weakness, fatigue and headache had developed, associated with a chronic cough, with occasional expectoration of blood-tinged sputum.

Because of these complaints, he came to the medical outpatient clinic on August 18. He was well nourished, although he had lost 12 pounds (5.4 Kg.), and was not acutely ill. The oral part of the pharynx was slightly injected, and he complained of pain in the right ear. The chest was symmetric, and expansion was equal but limited. The lungs were resonant, but the breath sounds were somewhat diminished. No rales were heard. The blood pressure was 100 systolic and 56 diastolic, the hemoglobin concentration 75 per cent and the white cell count 8,400, with 77 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes and 3 per cent eosinophils. The temperature, pulse rate and respiratory rate were normal. A Mantoux test gave no reaction, and a roentgenogram of the chest failed to reveal evidence of any pathologic condition (fig. 1A).

Loss of weight, fatigue and weakness continued, and the patient noticed pounding of the heart and some shortness of breath when he climbed stairs. About September 7 he fainted and remained unconscious for several minutes. He continued to attend school despite his illness, but fainted again on September 12. The next day he was unable to get out of bed and lost consciousness, remembering nothing until he awoke in the hospital.

As a child he had had measles, chickenpox and whooping cough, but had never been acutely ill and had recovered rapidly. He had been receiving treatment for congenital syphilis since childhood and had been given four injections of neoarsphenamine since August 1937, the last on September 2. There was no tuberculosis in his family, nor was any contact known. For six months before admission to the hospital he had been employed at a shoe-shining parlor, using a liquid dye with an acrid and unpleasant odor and fumes which often made him cough. He was convinced that the dye was responsible for his illness and said that he had always been well until he began to work at shoe dyeing.

Physical examination on September 13 showed a well developed, rather thin Negro, cyanotic and moderately dyspneic, with a temperature of 101.2 F. There was no rigidity of the neck, and no pupillary abnormalities. A small amount of blood-tinged sputum was noted in the posterior part of the pharynx. The respirations were rapid (42 per minute), irregular and shallow. The lungs were resonant throughout, and numerous medium crepitant rales were heard over both

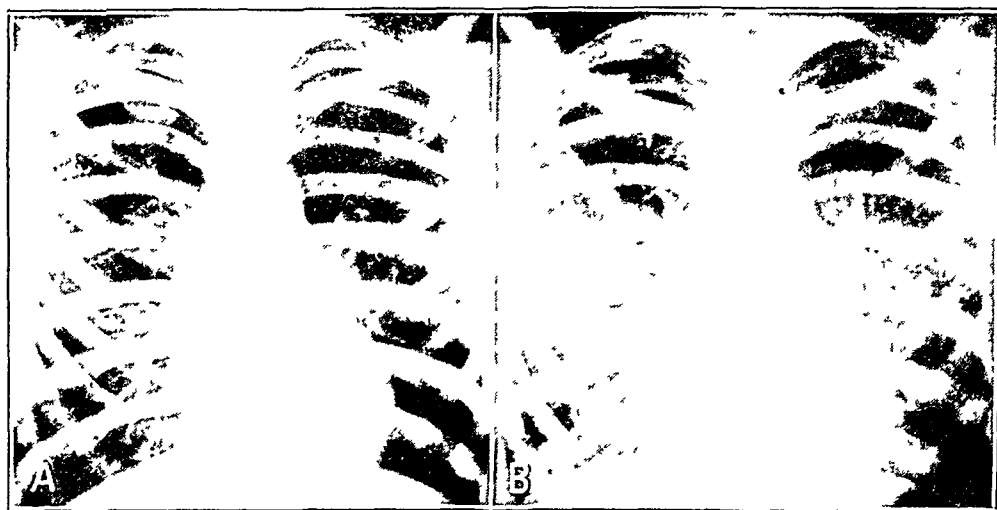


Fig. 1.—*A*, roentgenogram of the chest taken Aug. 18, 1937, interpreted as normal. *B*, roentgenogram taken September 14, showing uniform, soft, nodular infiltrations of both lung fields.

lung fields. The heart was not enlarged and was beating regularly at a rate of 120 per minute. A systolic murmur was heard at the apex, and the aortic second sound was louder than the pulmonic second sound. The abdomen was soft, and no masses or viscera were felt. The extremities were symmetric and the reflexes active and equal.

Three urinalyses showed specific gravities of 1.012, 1.012 and 1.016, a few to occasional red blood cells, occasional pus cells and very occasional granular casts, but no albumin or sugar. The hemoglobin concentration was 38 to 35 per cent, the red cell count 1,990,000 and the white cell count 8,000 to 16,000, with 79 per cent polymorphonuclear leukocytes, 16.5 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The Kahn reaction was weakly positive and the Wassermann reaction doubtful. Results of analysis of the spinal fluid were within normal limits. Four examinations of the sputum were made, but no acid-fast bacilli could be found. A roentgenogram of the chest

showed a soft, nodular infiltration of both lung fields, uniformly and extensively distributed, which was interpreted as miliary tuberculosis (fig. 1 *B*).

The patient was placed in an oxygen tent because of severe cyanosis and dyspnea and twenty-four hours later was so much improved that he felt comfortable out of the tent. On the second day of hospitalization his temperature rose to 104 F., but it fell to normal on the fourth day and was never significantly elevated thereafter. A transfusion was given, without apparent benefit. He coughed intermittently, occasionally raising blood-tinged sputum, and his respiratory rate was usually about 30 per minute. After the fourth day he was continually nauseated, vomited frequently and complained of epigastric pain. On the eighth day his respirations became shallow and labored, cyanosis returned and administration of oxygen was started again. He died on the ninth day.

At autopsy, the right lung weighed 800 Gm. and the left 720 Gm. Both were voluminous and exhibited uniformly diminished crepitation. The pleural surfaces and cut sections were coarsely granular because of innumerable uniformly distributed, tiny, translucent white nodules, measuring 1 to 2 mm. and surrounded by areas of injection. When these nodules were examined under a hand lens they were seen to be irregular, with fine white streaks extending from their centers into the adjacent parenchyma. They occurred about the terminal bronchioles, and in the centers of some a tiny lumen was seen. Careful search was made for Ghon tubercles, caseation, cavitation or scarring, without success. The hilar lymph nodes were slightly enlarged, edematous, pale and soft and on section showed hypertrophied follicles. The mucosa of the trachea and bronchi was slightly edematous and injected, but no areas of ulceration or necrosis could be found. The pulmonary vessels were smooth and elastic.

The right kidney weighed 160 Gm. and the left 200 Gm. They were slate-blue purplish and had tense capsules. The cortices were markedly thickened, and the same discoloration extended uniformly throughout the renal parenchyma.

Nodular lesions were not found in any organ except the lungs.

Microscopic examination revealed that the miliary nodules observed in the gross specimen were formed by lesions of the small bronchioles. In some the lumen was filled with fibrin, red blood cells and macrophages containing red blood cells and pigment; in others the epithelium was partly or totally desquamated, and the lumen was clogged by necrotic epithelial debris, fibrin and macrophages containing pigment and blood (fig. 2 *A* and *B*). This exudate showed various stages of organization. Frequently the bronchioles were almost filled with loose granulation tissue, sometimes growing in polypoid masses from one side of the injured bronchiole, without involving the remainder of its wall. Elsewhere, this connective tissue overgrowth proceeded symmetrically from the entire wall. In more advanced stages the bronchiole was completely obliterated by connective tissue and was recognizable only because small strips of smooth muscle could be seen in the periphery. The muscularis and elastic tissue fibers of the wall showed widespread destruction, with penetration and replacement by strands of connective tissue continuous with the fibrous tissue surrounding the involved bronchiole. Strips of connective tissue extended from the involved area into the adjacent parenchyma; in places the alveolar wall was thickened, and occasionally the alveolar space was occluded. There was evidence of extensive hemorrhagic pneumonia in most of the sections. Areas of atelectasis and emphysema were noted about some of the bronchioles. There was a greater proportion of severe than of mild involvement.

The kidneys showed acute diffuse hemorrhagic glomerulonephritis in an early stage. The pathologic change was for the most part proliferative, and frequently

the space between Bowman's capsule and the glomerulus was filled with blood. Epithelial crescents were not infrequent, and everywhere the tubules were packed with red blood cells.



Fig. 2.—*A*, photomicrograph of a diseased bronchiole, early stage, showing partial destruction of bronchiolar epithelium, obliteration of the lumen by fibrin and partial organization of the exudate. *B*, photomicrograph of a diseased bronchiole, late stage, showing almost complete destruction and replacement by dense connective tissue pierced by small capillaries.

COMMENT

This case had been clinically diagnosed as miliary tuberculosis. Chronic cough, expectoration of bloody sputum, progressive weakness, loss of weight and increasing dyspnea and cyanosis, together with a consistent roentgenologic picture, seemed to confirm this incorrect diagnosis. The history of working with a dye dissolved in a volatile solvent (impure trichloroethylene) was considered incidental, despite the patient's conviction that the dye was responsible for his illness. The clinical course was atypical for miliary tuberculosis in that the patient was moribund when first seen, improved rapidly and then suffered severe respiratory distress, forty-eight hours before death. Results of examination of the sputum showed nothing significant.

The absence of clinical or laboratory evidence of meningitis might have suggested another diagnosis. Leifer and Winkler¹⁶ were aided in making the correct diagnosis in their case by the results of an examination of the blood. They stated that patients with miliary tuberculosis usually have a relative leukopenia, an absolute lymphopenia and a diminution or lack of eosinophils. Their patient with bronchiolitis fibrosa obliterans had a leukocytosis, with an absolute increase in the lymphocyte count and from 10 to 12 per cent eosinophils. In our patient, however, the white cell count was elevated, with 16.5 per cent lymphocytes and only 2 per cent eosinophils. Furthermore, when his temperature fell to normal the leukocyte count was 8,000.

The rarity of bronchiolitis fibrosa obliterans is probably responsible for failure to recognize this disease during life. It is important to include bronchiolitis fibrosa obliterans among the possible diagnoses when confronted with violent respiratory distress of pulmonary origin. Then a careful review of the history may implicate a poisonous agent, a foreign body or a recently complicated acute or chronic infection. If the process produces incomplete closure of the bronchioles, emphysema results and is a differential aid of some value. When the course of illness falls into three stages, as described by Fraenkel,² bronchiolitis fibrosa obliterans is the most likely diagnosis.

In cases of interstitial pneumonia and miliary carcinomatosis the roentgenogram may be similar to that in cases of bronchiolitis fibrosa obliterans. However, interstitial pneumonia is not usually accompanied by the intense dyspnea and cyanosis associated with bronchiolitis fibrosa obliterans. In cases of miliary carcinomatosis the primary tumor can frequently be found and patients exhibit severe inanition, which contrasts with the well nourished appearance of victims of bronchiolitis fibrosa obliterans.

Bronchiolitis fibrosa obliterans is usually found in young patients, but Müller ⁷ reported typical microscopic lesions in 2 elderly persons. There is no sex predilection, except as determined by occupation.

SUMMARY

A review of the literature dealing with bronchiolitis fibrosa obliterans is presented, with reference to the etiology, the pathology, the clinical symptoms and the course of the disease.

The pathology, pathogenesis and end results are discussed with respect to the clinical picture.

A case history with autopsy observations is given.

Factors of importance in the differential diagnosis are outlined.

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ORIGIN OF KETONE BODIES FROM FATS AND THEIR REGULATION

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AND

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Of the three substances usually grouped under the term "ketone bodies," namely, acetoacetic acid, beta-hydroxybutyric acid and acetone, the second is not a ketone, and the third represents merely a breakdown product of its more physiologically significant precursors. It is now generally agreed that under conditions leading to ketosis acetoacetic acid is the first ketone body to be formed.¹ It is known that various tissues of the mammalian organism are able to reduce acetoacetic acid to beta-hydroxybutyric acid and also to effect the reverse reaction. The direction of this reversible reaction depends on the concentration of substrates present and on the oxygen tension, and there is evidence that an equilibrium between these two substances is established rapidly.² It is, therefore, a matter of practical importance in balance or recovery experiments to estimate the amounts of both of these substances present in the tissues when attempting to account for the fate of a given amount of either. Acetone is readily formed in solutions containing acetoacetic acid, and it is generally assumed that whenever it is found in biologic fluids it is merely a spontaneous decomposition product which indicates that an equivalent amount of one of the other ketone bodies was formerly present.

SITE OF ORIGIN OF THE KETONE BODIES

Practically all investigators have agreed as to the chief source of the ketone bodies which appear in the blood. Embden and associates³ and

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1. Jowett, M., and Quastel, J. H.: *Biochem. J.* **29**:2181, 1935.

2. Snapper, I., and Grünbaum, A.: *Biochem. Ztschr.* **181**:410 and 418, 1927. Jowett and Quastel.¹

3. Embden, G., and Kalberlah, F.: *Beitr. z. chem. physiol. u. path.* **8**:121, 1906. Embden, G., and Engel, H.: *ibid.* **11**:323, 1908.

later Snapper, Grünbaum and Neuberg⁴ perfused livers, kidneys, lungs and skeletal muscles and found that only the liver produced significant amounts of the ketone bodies. A similar conclusion regarding ketogenesis by these organs in situ was reached by Himwich, Goldfarb and Weller,⁵ who compared the ketone levels of the inflowing arterial blood and the outflowing venous blood of various organs in the intact animal. However, they found an occasional output of small amounts of ketone bodies from the skeletal muscles and the intestinal tract. In agreement with this, Jowett and Quastel⁶ found that slices of kidney, spleen, testis and brain could produce in vitro small amounts of the ketone bodies from butyric acid, although liver slices under similar conditions produced ten to forty times as much.

Whether or not the extrahepatic tissues can under special experimental conditions be shown to form some ketone bodies, it is clear that in the living intact animal the liver is practically the sole source for these substances. Thus it has been demonstrated that Eck fistula dogs do not exhibit increased ketosis on phlorhization.⁷ The reduction of hepatic function by hepatotoxic agents also decreases the rate of appearance of ketone bodies.⁸ Chaikoff and Soskin⁹ compared the rate of disappearance of administered sodium acetoacetate in intact and in eviscerated normal dogs and diabetic dogs and showed that the initial ketosis in intact diabetic animals was due to rapid ketogenesis in the liver. Finally, Mirsky¹⁰ has recently shown that the ketogenic effects of certain pituitary extracts which are regularly obtained in normal animals cannot be demonstrated in the absence of the liver.

SOURCE MATERIALS FOR PRODUCTION OF KETONE BODIES

The early work of Embden and co-workers¹¹ indicated the formation of extra ketones by the perfused livers with which they worked when fatty acids, certain amino acids or pyruvic acid was added to the perfusing fluid. These three different source materials for the ketone bodies have since been confirmed by a number of investigators in a

4. (a) Snapper, I.; Grünbaum, A., and Neuberg, J.: *Biochem. Ztschr.* **167**: 100, 1926. (b) Snapper, I., and Grünbaum, A.: *ibid.* **201**:464, 1928.

5. Goldfarb, W., and Himwich, H. E.: *J. Biol. Chem.* **101**:441, 1933. Himwich, H. E.; Goldfarb, W., and Weller, A.: *ibid.* **93**:337, 1931.

6. Jowett, M., and Quastel, J. H.: *Biochem. J.* **29**:2159, 1935.

7. Fischler, H., and Kossow, M.: *Deutsches Arch. f. klin. Med.* **111**:479, 1913.

8. Leites, S., and Odinow, A.: *Biochem. Ztschr.* **286**:93, 1936.

9. Chaikoff, I. L., and Soskin, S.: *Am. J. Physiol.* **87**:58, 1928.

10. Mirsky, I. A.: *Am. J. Physiol.* **115**:424, 1936.

11. Embden, G.; Salomon, K., and Schmidt, H.: *Beitr. z. chem. Physiol. u. Path.* **8**:129, 1906. Embden, G., and Marx, A.: *ibid.* **11**:318, 1908.

variety of ways.¹² However, Embden and associates reported that the amount of ketone bodies arising from fat greatly exceeded that from the other sources. Subsequent work has emphasized the fact that when ketosis occurs in the living organism it may be regarded, for practical purposes, as an index of the catabolism of fat. Thus the perfused fatty liver produces many more ketones than the liver which is poor in fat.¹³ The livers of depancreatized or phlorhizinized animals, which are characteristically rich in fat, are known to produce excessive amounts of ketone bodies.¹⁴ In the intact normal animal the feeding of fat or the excessive use of depot fat induced by starvation results in ketosis. More recently, Stadie, Zapp and Lukens¹⁵ have demonstrated that the production of ketones by liver slices *in vitro* is accompanied by the disappearance of amounts of fatty acid sufficient to account for more than one mol of ketone per mol of fatty acid.

MECHANISM OF PRODUCTION OF KETONE BODIES

The general conception of the mechanism by which ketones are formed from fatty acids seemed for a long time to be quite settled, but it has recently undergone at least two metamorphoses. The theory of successive beta oxidation originated from the work of Knoop.¹⁶ It was based on the feeding of various phenyl-substituted fatty acids to test animals and the identification of the excretion products in the urine. The administration of either benzoic, phenylpropionic or phenylvaleric acid resulted in the appearance of hippuric acid. After the administration of phenylacetic and phenylbutyric acids, phenylaceturic acid appeared in the urine. These results could be reasonably explained only by assuming that the fatty acids were degraded by the splitting off of two carbon atoms at a time, by oxidation at the carbon atom which occupied the beta position to the carboxyl group. It was assumed that the acetic acid molecules so formed were rapidly metabolized and the phenyl group was left attached to one or two carbon atoms, depending on the original number of carbon atoms in the fatty acid molecule. This assumption was confirmed *in vivo* by Dakin and was extended to the *in vitro* oxidation of various fatty acids by hydrogen peroxide at

12. (a) Cohen, P. P.: *J. Biol. Chem.* **119**:333, 1937. (b) Edson, N. L.: *Biochem. J.* **29**:2082, 1935; (c) **29**:2498, 1935. (d) Jowett and Quastel⁶; (e) footnote 1. (f) Leloir, L. F., and Muñoz, J. M.: *Biochem. J.* **33**:734, 1939.

13. Raper, H. S., and Smith, E. C.: *J. Physiol.* **62**:17, 1926.

14. Embden, G., and Lattes, L.: *Beitr. z. chem. Physiol. u. Path.* **11**:327, 1908.

15. Stadie, W. C.; Zapp, J. A., and Lukens, F. D. W.: *J. Biol. Chem.* **137**:75, 1941.

16. Knoop, F.: *Beitr. z. chem. Physiol. u. Path.* **6**:150, 1905.

had passed. Thus Hurtley¹⁸ sought for the butyric and acetic acids which would be expected to be present in the liver during active ketogenesis and failed to find them. Clutterbuck and Raper,¹⁹ Smedley-MacLean and associates,²⁰ Witzeman²¹ and Verkade and van der Lee,²² who repeated and extended the *in vitro* work of Dakin, found that while beta oxidation did occur, oxygen could also become attached at the alpha and gamma positions. A more serious objection from the point of view of the whole animal was the observation by Deuel and associates²³ that more ketone bodies arose in an animal fed octanoic acid than in an animal fed an equimolar amount of butyric acid. Shortly afterward, Jowett and Quastel,²⁴ and later Leloir and Muñoz,^{12f} observed that the amounts of ketone bodies formed by liver slices *in vitro* could not be accounted for on the assumption that only the last four carbon atoms of each fatty acid molecule gave rise to a ketone body. A similar discrepancy was reported for perfused livers by Blixenkrone-Møller²⁵ and for liver slices *in vitro* by Stadie and co-workers²⁶ when the oxygen consumption during experiments was compared with that which would have been expected on the basis that all but the last four carbon atoms of each fatty acid were being disposed of by the oxidation of the acetic acid formed. The observed oxygen consumptions were far smaller than would allow for this mode of fatty acid breakdown. Finally, the improved technics for ketone estimation, which have made possible the determination of relatively small amounts in blood and tissue, have led to the recent finding that the odd-numbered fatty acids also give rise to smaller but significant amounts of the ketone bodies as compared with the even-numbered fatty acids. This has been reported by Jowett and Quastel,²⁴ Edson²⁷ and Leloir and Muñoz^{12f} for isolated tissue (liver) and by MacKay and associates²⁸ for the intact animal.

18. Hurtley, W. H.: *Quart. J. Med.* **9**:301, 1916.

19. Clutterbuck, P. W., and Raper, H. S.: *Biochem. J.* **19**:385, 1925.

20. Ponsford, A. P., and Smedley-MacLean, I.: *Biochem. J.* **28**:892, 1934. Smedley-MacLean, I., and Pearce, M. S. B.: *ibid.* **28**:486, 1934.

21. Witzeman, E. J.: *J. Biol. Chem.* **107**:475, 1934.

22. Verkade, P. E., and van der Lee, J.: *Ztschr. f. physiol. Chem.* **227**:213, 1934.

23. Butts, J. S.; Cutler, C. H.; Hallman, L., and Deuel, H. J.: *J. Biol. Chem.* **109**:597, 1935. Deuel, H. J., Jr.; Hallman, L. F.; Butts, J. S., and Murray, S.: *ibid.* **116**:621, 1936.

24. Jowett and Quastel (footnotes 1 and 6).

25. Blixenkrone-Møller, N.: *Ztschr. f. physiol. Chem.* **252**:117 and 137, 1938.

26. Stadie, W. C.; Zapp, J. A., and Lukens, F. D. W.: *J. Biol. Chem.* **132**:423, 1940.

27. Edson, N. L.: *Biochem. J.* **30**:1862, 1936.

28. MacKay, E. M.; Wick, A. N., and Barnum, C. P.: *J. Biol. Chem.* **136**:503, 1940.

It is obvious that the hypothesis of successive beta oxidation in the aforementioned form is no longer tenable. Indeed, as long ago as 1916 Hurltley¹⁸ proposed the theory of multiple alternate oxidation to account for his failure to find butyric and acetic acids in ketone-producing livers. He expressed the opinion that the intact fatty acid chain was first oxidized at each alternate carbon atom and then split into blocks of four carbon atoms each, a process which would not necessitate even the transient presence of either of the substances for which he tested. According to this hypothesis, the number of ketone molecules arising from a fatty acid would be the whole portion of the quotient if the number of carbon atoms in the fatty acid molecule is divisible by 4. This hypothesis was adopted by Deuel, Quastel, Leloir, Blixenkrone-Møller and Stadie, since it accounted for the greater than 1:1 ratio of ketogenesis from the higher fatty acids, the lower oxygen consump-

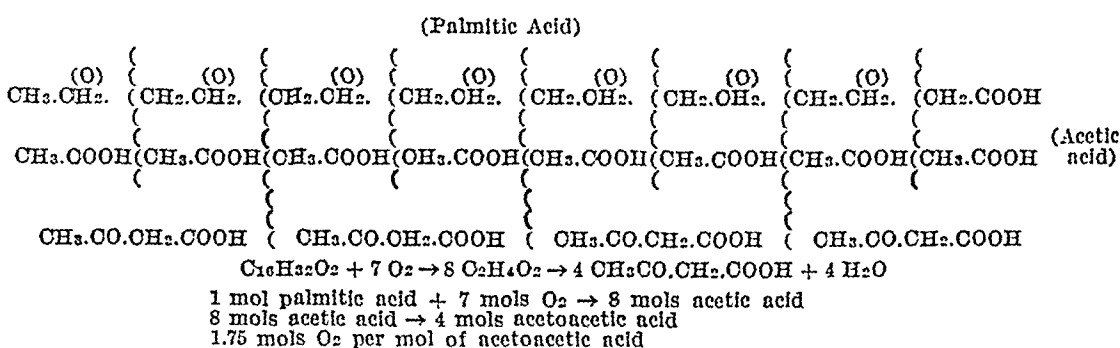
TABLE 2.—*Theory of Multiple Alternate Oxidation (Hurtley)*

(Palmitic Acid)			
$\text{CH}_3 \cdot \overset{\text{(O)}}{\text{CH}_2} \cdot \text{CH}_2 \cdot \overset{\text{(O)}}{\text{CH}_2} \cdot \left\{ \begin{array}{l} \overset{\text{(O)}}{\text{CH}_2} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \overset{\text{(O)}}{\text{CH}_2} \cdot \left\{ \begin{array}{l} \overset{\text{(O)}}{\text{CH}_2} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \overset{\text{(O)}}{\text{CH}_2} \cdot \left\{ \begin{array}{l} \overset{\text{(O)}}{\text{CH}_2} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \overset{\text{(O)}}{\text{CH}_2} \cdot \text{COOH} \\ \text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{COOH} \end{array} \right\} \end{array} \right\} \end{array} \right\}$			
$\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{COOH}$	$\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{COOH}$	$\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{COOH}$	$\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{COOH}$
$\text{C}_{16}\text{H}_{32}\text{O}_2 + 7 \text{ O}_2 \rightarrow 4 \text{ CH}_3\text{CO} \cdot \text{CH}_2 \cdot \text{COOH} + 4 \text{ H}_2\text{O}$			
1 mol palmitic acid + 7 mols $\text{O}_2 \rightarrow$ 4 mols acetoacetic acid			
(No butyric or acetic acid appears at any stage of the reaction)			
1.75 mols O_2 per mol of acetoacetic acid			

tion than that expected from the 1:1 ratio and the formation of ketone bodies from odd-numbered fatty acids.

Until recently the multiple alternate oxidation theory was adequate to explain the available data. However, it implied a phenomenon rather difficult to explain on biochemical grounds. The simultaneous oxidation of every alternate carbon atom offered no difficulty, but how should one explain the selective splitting of the molecule at every second keto group instead of at every keto group? This difficulty is avoided by a newer conception, which also accounts for other recent evidence not compatible with the theory of multiple alternate oxidation. In a systematic *in vitro* study of the ketogenic properties of fatty acids consisting of one to eleven carbon atoms, Jowett and Quastel²⁴ noted, among other things, ketone production from valeric acid (five carbon atoms) and a greater production of ketones from hexanoic acid than from butyric acid. Since valeric acid is known to give rise to sugar through propionic acid, one can account for the ketone formation only by assuming a condensation of a two carbon atom fragment from one molecule of valeric acid with a

similar two carbon atom fragment from another molecule. The condensation of such two carbon atom fragments (acetic acid) could also account for the greater ketone formation from hexanoic than from butyric acid. Leloir and Muñoz^{12f} recently confirmed these findings of Jowett and Quastel, and not long ago MacKay and co-workers²⁹ performed feeding experiments on intact animals the results of which supported the aforementioned interpretation and led the authors to postulate a new theory, which they have termed the " β oxidation-acetic acid condensation hypothesis." They found, in brief, that the feeding of propionic acid to their animals led to an accumulation of glycogen in the liver without formation of ketone bodies. The feeding of valeric acid led both to accumulation of the one and formation of the other. Heptanoic acid gave rise to glycogen and to more ketones than did valeric acid. MacKay and associates postulated that all fatty acid chains,

TABLE 3.—*Beta Oxidation—Acetic Acid Condensation (MacKay)*

whether odd or even numbered, were subjected to oxidation at each alternate carbon atom. However, the molecule then split at every keto group to form a number of acetic acid molecules, except where a three carbon atom fragment remained to form propionic acid (this procedure, of course, suggests in part the original beta oxidation theory, although there is little basis for deciding between successive and simultaneous oxidation and splitting). Ketones are formed by the condensation of two molecules of acetic acid, a process which has been known since the days of Friedmann.³⁰ The hypothesis of MacKay and co-workers seems to be the most reasonable explanation of the known facts at present.

REGULATION OF THE KETONE BODIES

For practical purposes the liver may be regarded as the chief, if not the only, source of ketone bodies in the intact organism. The extent to

29. MacKay, E. M.; Barnes, R. H.; Carne, H. O., and Wick, A. N.: J. Biol. Chem. **135**:157, 1940. MacKay, Wick and Barnum.²⁸

30. Friedmann, E.: Biochem. Ztschr. **55**:436, 1913.

which ketones accumulate in the blood or are excreted in the urine will, of course, depend on whether they can be disposed of by the extra-hepatic tissues and how rapidly such utilization may occur. Some of the earlier investigators regarded the ketone bodies as abnormal intermediary products of fat metabolism, which appeared only when there was a failure in carbohydrate oxidation. It was thought that under these circumstances the ketones could not be metabolized because of the supposed absence of a coupled oxidation phenomenon which ordinarily occurred.³¹ It is now well recognized that ketosis occurs under conditions in which large amounts of carbohydrate are being oxidized, and indeed it has been impossible to demonstrate any relation between the degree of ketosis and the rate of carbohydrate oxidation.³² On the other hand, there is ample evidence that both acetoacetic acid and betahydroxybutyric acid are catabolized to carbon dioxide and water by kidney, muscle, heart, brain, testis, etc., as tested on isolated slices *in vitro*.³³ Similar evidence is available for perfused whole organs, such as muscles or kidneys.³⁴ The rate of utilization of the ketone bodies by the normal intact organism has been estimated by a number of investigators.³⁵ It is important to note that this utilization, at the blood concentrations of ketones ordinarily found in clinical ketosis, may constitute a highly significant portion of the total energy requirements of the organism. Indeed, it has been estimated that the ketone utilization in the animals which have been studied could account for 50 to 80 per cent of the total oxygen consumption.

This large normal capacity for the utilization of ketones makes it probable that even the small amounts normally found in the blood indicate that the normal liver forms and continues to secrete ketone bodies into the blood.³⁶ It might be supposed, however, that the severe ketosis of diabetes, phlorhizin poisoning or starvation is the result of

31. Shaffer, P. A.: Harvey Lectures, 1922-1923, Baltimore, Williams & Wilkins Company, 1923, p. 95.

32. (a) Dye, J. A., and Chidsey, J. L.: *Am. J. Physiol.* **127**:745, 1939. (b) Friedemann, T. E.: *J. Biol. Chem.* **116**:133, 1936. (c) Mirsky, I. A., and Broh-Kahn, R. H.: *Am. J. Physiol.* **119**:734, 1937. (d) Waters, E. T.; Fletcher, J. P., and Mirsky, I. A.: *ibid.* **122**:542, 1938.

33. Edson, N. L., and Leloir, L. F.: *Biochem. J.* **30**:2319, 1936. Jowett and Quastel (footnotes 1 and 6). Stadie, Zapp and Lukens.²⁶

34. (a) Blixenkrone-Møller, N.: *Ztschr. f. physiol. Chem.* **253**:261, 1938. (b) Snapper, I.; Grünbaum, A., and de Leon, M.: *Biochem. Ztschr.* **201**:473, 1928.

35. Barnes, R. H.; Drury, D. R.; Greeley, P. O., and Wick, A. N.: *Am. J. Physiol.* **130**:144, 1940. Wick, A. N., and Drury, D. R.: *J. Biol. Chem.* **138**:129, 1941.

36. Crandall and associates (Crandall, L. A.; Ivy, H. B., and Ehni, G. J.: *Am. J. Physiol.* **131**:10, 1940) differ from this opinion on the basis of experiments with the London cannula technic.

some difficulty in the utilization of ketones by the periphery, with or without a greater production by the liver. This possibility has been tested both *in vitro* and *in vivo*, without confirmation. Chaikoff and Soskin⁹ and others³⁷ have shown that the peripheral tissues of the diabetic organism dispose of the ketone bodies as rapidly as do those of the normal animal. With the possible exception of the adrenalectomized animal,³⁸ it must be assumed that whenever ketones appear in excess in the blood and other tissues, this condition is due to a rate of formation and secretion by the liver sufficiently rapid to exceed even the large disposal capacity of the periphery. It is thus no longer proper to speak of antiketogenesis in the sense so long employed by clinicians, by which they actually meant ketolysis. In view of present knowledge, the various ketogenic and antiketogenic ratios³¹ which have been used to calculate the amounts of carbohydrate "necessary for the oxidation of the ketone bodies" must be regarded as being without any real significance. The former clinical utility of these rule of thumb ratios was purely coincidental.

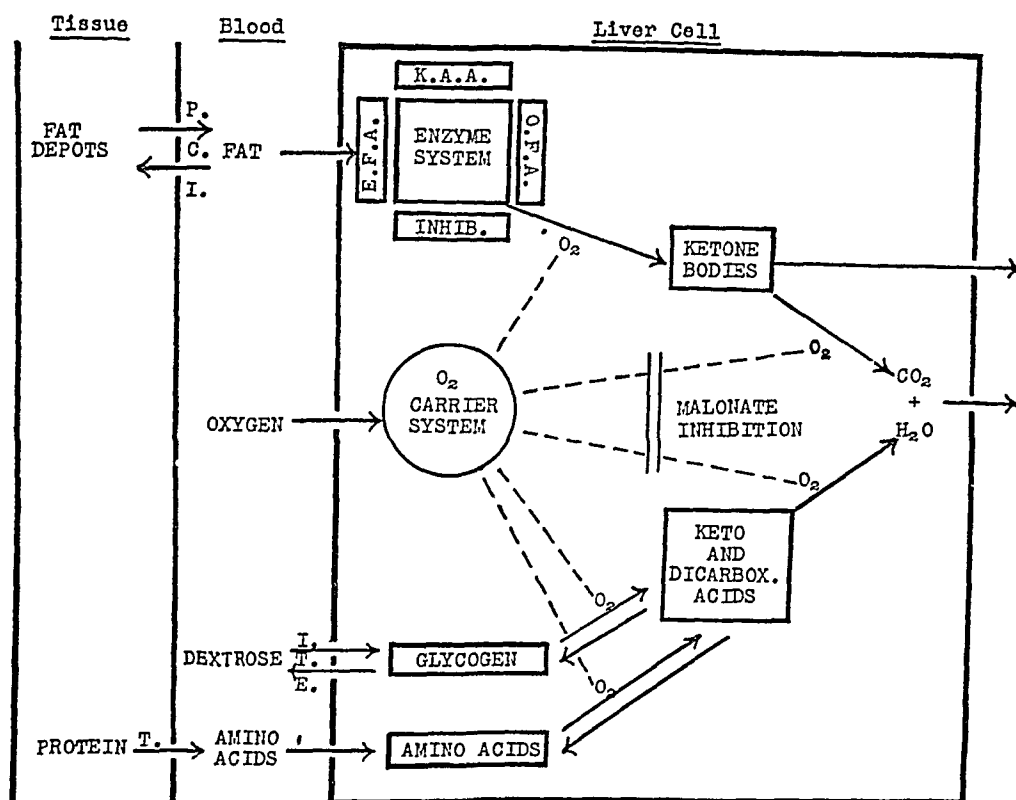
It is clear that the regulation of the ketone bodies in the intact organism must depend on factors which either increase or decrease the rate of formation of these substances by the hepatic cells, as indeed the terms ketogenesis and antiketogenesis imply. It is necessary, therefore, to interpret those conditions or substances which increase or decrease ketosis in terms of their effects on the liver. The commonest conditions under which significant ketosis occurs are starvation in the normal organism and experimental or clinical diabetes. Carbohydrate is the chief antiketogenic foodstuff, while protein is relatively less effective. If one considers the simple outlines of the conditions governing the metabolism of an hepatic cell, one must include the substrates available for its metabolism, the availability of enzymes for the oxidation of those substrates and the capacity of the oxygen carrier systems of the cells. From this point of view it is not difficult to account for the ketogenic influence of starvation and diabetes. Both conditions are accompanied by low levels of liver glycogen. Whether or not the glycogen level itself is the critical factor, or is merely a reflection of increased glycogenolysis,³⁹ it may be supposed that under these conditions carbohydrate yields to fat as the chief substrate for oxidation. This might be regarded as a simple mechanical result—the fat filling the space no

37. Blixenkrone-Møller.^{34a} Friedemann.^{32b} Snapper, Grünbaum and de Leon.^{34b} Stadie, Zapp and Lukens.²⁶

38. Nelson, N.; Grayman, I., and Mirsky, I. A.: *J. Biol. Chem.* **132**:711, 1940.

39. (a) Mirsky, I. A.; Korenberg, M.; Nelson, N., and Nelson, W. E.: *Endocrinology* **28**:358, 1941. (b) Shapiro, I.: *J. Biol. Chem.* **108**:373, 1935. (c) Somogyi, M.: *Proc. Soc. Exper. Biol. & Med.* **45**:644, 1940.

longer occupied by glycogen—or might perhaps be more accurately described as the establishment of the predominance of fat in the competition for available oxygen, according to the evidence brought forward by Edson²⁷ and by Jowett and Quastel.²⁴ The antiketogenic action of protein may be similarly explained in accordance with its glycogenic and lipotropic properties. The inferior antiketogenic potency of protein as compared with carbohydrate may depend on the fact that some of its constituent amino acids are ketogenic and also on another phenomenon, which has been experimentally demonstrated but which is difficult to explain. Edson⁴⁰ has shown that ammonia is ketogenic and that the



Factors influencing the rate of formation of the ketone bodies by the liver cell. The following abbreviations have been employed: *P*, the anterior pituitary factor; *C*, the adrenal cortical factor; *I*, insulin; *T*, the thyroid hormone; *E*, epinephrine; *E.F.A.*, fatty acids with an even number of carbon atoms; *O.F.A.*, fatty acids with an odd number of carbon atoms; *K.A.A.*, ketogenic amino acids, and *Inhib.*, substances which have "active groups" similar to those of fatty acids and which therefore inhibit ketogenesis by competition for the enzyme, e. g., benzoic acid and alphaaminobutyric acid. The malonate inhibition which is indicated is ketogenic in effect by decreasing the competition for available oxygen in favor of the reaction: fatty acids \rightarrow ketone bodies.

ammonia produced by the deamination of amino acids acts similarly to exogenous ammonia. Hence, when amino acids form a larger proportion

40. Edson (footnotes 12 *b* and *c*).

of the substrates of the liver cell the increased amount of ammonia liberated may play a role in stimulating ketogenesis.

The work of Jowett and Quastel⁶ and of Cohen^{12a} has suggested another type of mechanism for antiketogenesis, namely, competition for the enzyme system concerned with the conversion of fatty acids to ketones. These workers have shown that certain substances with "active" groups similar to those possessed by the even-numbered fats may attach themselves to and thus compete for this enzyme system. If these substances themselves produce no ketones, or less ketones than are produced by equimolar amounts of the even-numbered fats, the net result will be a diminution of ketogenesis, even though some of these substances would themselves be ketogenic in action if given at a time when the enzyme system was unoccupied. Such substances are: odd-numbered fatty acids; certain amino acids, and benzoic, cinnamic, and alphaaminobutyric acids. The type of inhibition which they exert is somewhat analogous to the well known action of malonate on the succinodehydrogenase system.

ENDOCRINE REGULATION OF THE KETONE BODIES

Knowledge of the endocrine regulation of the ketone bodies is as yet fragmentary. Practically every endocrine gland can be involved on the basis of one or another piece of evidence, but such links are usually vague. Thus Deuel and co-workers⁴¹ have shown a sex difference in rats as regards the degree of ketosis manifested under similar conditions, from which one might conclude that the gonads perform some unknown function. It may be, of course, that this sex difference depends on the sexual variation in the activity of the anterior lobe of the pituitary gland and is not a direct result of gonadal activity. It is also known that both the thyroid gland⁴² and the secretion of the adrenal medulla⁴³ exert a ketogenic influence. The actions have been observed chiefly under conditions in which the administration of an extract of the adrenal medulla or of thyroid has aggravated ketosis resulting from other circumstances. Since both these substances increase the rate of hepatic glycogenolysis, their ketogenic action may be perhaps regarded as being secondary to this phenomenon. At any rate, no mechanism for a more direct action is known.

Of the endocrine factors involved, the three about which there is some definite information are, on the one hand, insulin, which is anti-ketogenic, and, on the other hand, the anterior pituitary factor and the

41. Deuel, H. J., Jr.; Hallman, L. F., and Murray, S.: *J. Biol. Chem.* **119**: 257, 1937. Grunewald, C. F.; Cutler, C. H., and Deuel, H. J., Jr.: *ibid.* **105**:35, 1934.

42. Mirsky, I. A., and Broh-Kahn, R. H.: *Am. J. Physiol.* **117**:6, 1936.

43. Hubbard, R. S.: *J. Biol. Chem.* **49**:385, 1921.

adrenal cortical factor, which are ketogenic. That the pancreas and the anterior lobe of the pituitary are truly antagonistic in action as regards ketosis seems clear from the following facts:

1. Extract of the anterior lobe of the pituitary will cause a rise in the ketone bodies of the blood even in the normal animal, in which amounts of insulin adequate for ordinary purposes are present.⁴⁴

2. The administration of additional insulin to a normal animal prior to the administration of extract of the anterior lobe of the pituitary diminishes or abolishes the ketosis which would otherwise be precipitated.⁴⁴

3. The action both of insulin and of the extract of anterior lobe of the pituitary in regard to ketosis has been shown to be exerted largely on the liver, since neither is effective in the liverless animal.⁴⁵

It must be concluded that here again the regulatory action is on the production of ketone bodies and not on their utilization.

The pancreas and the anterior lobe of the pituitary body also exert opposing actions on a phenomenon outside the liver which probably has an important effect on ketogenesis, namely, the mobilization of fat from the peripheral depots. The human being with uncontrolled diabetes and the depancreatized animal without lipocaic deficiency both exhibit hyperlipemia and fatty infiltration of the liver. The administration of insulin inhibits this mobilization of fat to the liver.⁴⁶ On the other hand, certain extracts of the anterior lobe of the pituitary gland have been shown to cause hyperlipemia by liberation of fat from the depots.^{46a} Thus, insulin and the anterior lobe of the pituitary body might be supposed not only to exert opposing influences on the hepatic catabolism of fat to ketone bodies but to regulate the supply of fat to the liver for this catabolism. However, the intimate nature of the chemical mechanisms involved in these actions is unknown, and there is a possibility that at least a portion of these effects is indirect, through changes in carbohydrate metabolism. Thus, insulin, which raises the liver glycogen in the diabetic animal, simultaneously inhibits ketosis. In the normal animal, in which insulin usually causes a fall in liver glycogen, it may also stimulate ketosis.^{39c} As regards the pituitary gland, there is some evidence that a continued high carbohydrate intake depresses its activity.⁴⁷ It is thus possible that the lack of carbohydrate intake in the

44. (a) Houssay, B. A.: *New England J. Med.* **214**:961, 1936. (b) Mirsky, I. A.: *Am. J. Physiol.* **116**:322, 1936.

45. Mirsky (footnotes 10 and 44 b).

46. Banting, F.; Best, C. H.; Collip, J. B.; Macleod, J. J. R., and Noble, E. C.: *Tr. Roy. Soc. Canada* **16**:27, 1922.

46a. Campbell, J., and Keenan, H. C.: *Am. J. Physiol.* **131**:27, 1940.

47. Soskin, S.; Mirsky, I. A.; Zimmerman, L. M., and Heller, R. C.: *Am. J. Physiol.* **116**:148, 1936.

fasting animal leads to an increased activity of the anterior lobe of the pituitary gland and that this in turn is responsible for both the lipemia and the ketosis of fasting.

As regards the adrenal cortex, about all that one can say at present is that it acts similarly to the anterior lobe of the pituitary gland. Since large amounts of extracts of each of these glands have been shown to be effective in the absence of the other gland, the bodies may act independently of each other. However, the striking lack of ketosis in the hypophysectomized animal does indicate the predominating influence of the pituitary gland over the adrenal cortex in the over-all regulation of the intact animal.⁴⁸

We may summarize by saying that the ketone bodies are probably normal intermediates of fatty acid catabolism in the liver. They appear in excess in the blood whenever the hepatic metabolism of fat is sufficiently speeded up, either by a lack of carbohydrate substrate or by a disturbance in the normal regulation of the substrate mixture. The ketone bodies are readily utilized by the peripheral tissues, under practically all known conditions. It remains for future workers to determine to what extent the derivation of energy from fat under various conditions proceeds through these physiologically important substances.

48. Long, C. N. H., and Lukens, F. D. W.: *J. Exper. Med.* **63**:465, 1936.
Mirsky, I. A.: *Science* **88**:332, 1938.

ACROPACHYDERMA WITH PACHYPERIOSTITIS

REPORT OF A CASE

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A systemic overgrowth of bones and skin may be caused by the abnormal function of certain endocrine glands, such as the anterior lobe of the hypophysis and the gonads. While certain characteristic forms, like acromegaly and gigantism, are clearly recognizable, other anomalies are less well defined.

This paper is devoted to the description of a disturbance in growth which is characterized by clubbing and squaring of the extremities, thickening of the skin over the face, scalp and extremities, and deformities of the long bones and their periost. Isolated descriptions of this condition have been reported under a variety of names—pseudoacromegaly, acromegalism, cutis verticis gyrata with acromegaly, pachyacria, megalia cutis et ossium, generalized hyperostosis and *pachydermie plicaturée avec pachypériostose des extrémités*. They all, however, deal with one and the same condition, which can and should be clearly differentiated from similar but unrelated conditions, particularly acromegaly, leprosy and pulmonary osteoarthropathy (Marie).

Because it produces such a strange disfiguration of the face, hands and feet, this condition, though rare, had attracted the attention of clinicians even before Marie and Souza-Leite¹ recognized the characteristic features of acromegaly. Friedreich² observed two brothers, Wilhelm and Karl Hagner, in whom an abnormal overgrowth of the hands and feet had developed at the age of 15. This disturbance later spread to the forearms, ankles, spine and face. Except for some discomfort in their legs and feet, both brothers were at the time of examination physically well. Friedreich called this condition "hyperostosis of the whole skeleton."

Twenty years later Wilhelm Hagner had wasting and general weakness as the result of bronchiectasis. Karl, on the other hand, remained

From the Joseph H. Pratt Diagnostic Hospital, a Unit of the New England Medical Center.

1. Marie, P., and Souza-Leite: *Essays on Acromegaly*, translation, London, New Sydenham Society, 1891.

2. Friedreich, N.: *Virchows Arch. f. path. Anat.* **43**:63, 1868.

healthy. Friedreich's successor, Erb,³ who examined both brothers, found a moderate additional increase in the overgrowth of the hands, feet, spine and maxillas. Although he attributed this enlargement to acromegaly, he was nevertheless aware that some of the distinctive features of that condition—prognathic jaw, headache and visual disturbances—were absent. Wilhelm H. died soon afterward from bronchiectasis and pneumonia. In his report of the autopsy, Arnold⁴ shared Erb's opinion about the presence of true acromegaly. He was also faced with Erb's difficulty, namely, that of explaining the lack of characteristic signs of acromegaly. He found the hypophysis, which was then not fully recognized as the source of acromegaly, macroscopically normal. The bones, especially those of the hands and feet, "were thickened and covered by periostitic new formation" but were not enlarged. The jaw was not particularly increased. The internal organs were also normal in size. The outstanding change was the abnormal periosteal overgrowth involving the whole spine, the pelvis, the clavicles and the extremities. Marie himself had difficulty in classifying these observations. Originally¹ he thought that these manifestations represented acromegaly. Later, when he recognized that clubbing and enlargement of the hands and feet occur in patients with certain pulmonary diseases, he classified the conditions of these 2 brothers as osteoarthropathy.⁵ Sternberg,⁶ however, in his comprehensive monograph on acromegaly, clearly distinguished their conditions from acromegaly, as well as from osteoarthropathy. He classified them as a new clinical entity. Yet as late as 1938 the name familial acromegaly was used by Renander,⁷ who otherwise recognized that the conditions of these brothers displayed some unusual aspects.

Tournier⁸ published a similar observation of this syndrome, which he designated as *maladie hypertrophiante singulière: lésions élephantiasiques des parties molles et du squelette*. Jadassohn⁹ described patients with thickening and furrowing of skin. This disturbance was called by Unna¹⁰ *cutis verticis gyrata*. Soon it became evident that some patients with *cutis verticis gyrata* showed enlargement of the hands and feet as well. These combined findings were reported in dermatologic

3. Erb, W.: *Deutsches Arch. f. inn. Med.* **42**:294, 1888.

4. Arnold, J.: *Beitr. z. path. Anat. u. z. allg. Path.* **10**:1, 1891.

5. Marie, P.: *Rev. de méd.* **10**:1, 1890.

6. Sternberg, M.: *Acromegaly*, translated by F. R. B. Atkinson, London, New Sydenham Society, 1899.

7. Renander, A.: *Acta med. Scandinav.* **96**:186, 1938.

8. Tournier: *Province méd.*, May 1891; cited by Touraine, Solente and Golé.^{25b}

9. Jadassohn, J.: *Verhandl. d. deutsch. dermat. Gesellsch.* (1906) **9**:451, 1907.

10. Unna, P. G.: *Monatsh. f. prakt. Dermat.* **14**:277; 1907.

and medical journals as instances of "cutis verticis gyrata and acromegaly" (Stuehmer,¹¹ Bruck,¹² Bassett-Smith,¹³ Weber,¹⁴ Ota¹⁵ and Naumann¹⁶). Leva¹⁷ and Sicard and Haguenau¹⁸ observed familial occurrence in two, and Oehme¹⁹ in three, members of one family, respectively. Apert and Bigot²⁰ (1921) described extensive periostitis over the long bones, revealed by roentgen examination in a case in which they classified the condition as typical osteoarthropathy. When they examined the patient ten years later no visible progression in the lesions was observed. Groenberg²¹ called attention to the presence of endocrine disturbances in 1 of his patients. The first diagnosis was leprosy. The patient was later carefully examined with roentgen rays by Renander,²² who found that the long bones showed characteristic changes, which he could verify in a second patient.²³ Inclined to consider these changes as the result of acromegaly, Renander determined the volume of the enlarged extremities by measuring their water replacement before and after irradiation of the hypophysis with roentgen rays. There was some regression in volume after irradiation. His findings, however, are not convincing; furthermore, it has never been possible, even after successful operations, to reduce acromegalic overgrowth once it has developed.

Bussalai²⁴ reported an instance of an advanced state of this disease. His paper contained a description of results of a biopsy of the skin. After many isolated observations the entity of this syndrome was finally recognized by the French authors Touraine, Solente and Golé.²⁵ They named it *pachydermie plicaturée avec pachypériostose des extrémités*. None of these studies, however, received notice in the United States.

11. Stuehmer, H.: Dermat. Wchnschr. **77**:249, 1922.

12. Bruck: Dermat. Wchnschr. **81**:1061, 1925.

13. Bassett-Smith, P. W.: Proc. Roy. Soc. Med. (Clin. Sect.) **18**:23, 1925.

14. Weber, F. P.: Brit. J. Dermat. **40**:1, 1928.

15. Ota, M.: Dermat. Wchnschr. **92**:345, 1931.

16. Naumann, H.: Arch. f. Dermat. u. Syph. **154**:595, 1928.

17. Leva, J.: Med. Klin. **11**:1266, 1915.

18. Sicard, J. A., and Haguenau: Bull. et mém. Soc. méd. d. hôp. de Paris **73**:1238, 1914.

19. Oehme, C.: Deutsche med. Wchnschr. **45**:207, 1919.

20. Apert and Bigot: Bull. et mém. Soc. méd. d. hôp. de Paris **45**:1715, 1921.

21. Groenberg, A.: Acta med. Scandinav. **67**:24, 1927.

22. Renander, A.: Acta radiol. **18**:652, 1937.

23. Renander, A.: Acta radiol. **19**:254, 1938.

24. Bussalai, L.: Gior. ital. di dermat. e sif. **71**:1066, 1930.

25. (a) Golé, L.: Un syndrome osteo-dermopathique. Thesis, Paris, 1935.
(b) Touraine, A.; Solente, G., and Golé, L.: Presse méd. **43**:1820, 1935.

My interest in this syndrome was aroused after observing a man studied twenty years ago by Sisson, who at that time published a clinical note entitled "*Cutis Verticis Gyrata*,"²⁶ The coincidence of *cutis verticis gyrata* with what he called *acromegaly* puzzled him. His report, however, was mainly concerned with the results of an operation on the patient's thickened eyelids.

REPORT OF CASE

M. C., a shoemaker, was born in Italy in 1896. His parents and three brothers were healthy and free from any disease of the bones, joints or skin. His childhood was uneventful, and physically and mentally he was normal. At the age of 17 he first noticed an increase in size of his fingers and toes, which soon reached unusual proportions. Since this enlargement caused no pain he was able to start work as a shoemaker without difficulty. His only complaint was a marked tendency to sweat. When he was 19 his forehead became increasingly furrowed. At the age of 23 he noticed a gradual increase in the size and heaviness of both upper eyelids. This finally reached such proportions that he entered the Eye and Ear Infirmary of the Massachusetts General Hospital on Nov. 25, 1924. According to Sisson's report, the patient's sight was considerably impaired by enlarged upper lids. The vision in both eyes was 20/30. In addition to the ptosis, the skin over the forehead showed deep transverse folds and furrows, as well as oily secretions. His hair was coarse and abundant. Roentgen examination showed a normal pituitary gland. "There was characteristic clubbing of the terminal phalanges. In addition the outline of the lower end of the radius and ulna was somewhat irregular, suggesting periosteal proliferation. The tibia and fibula were considerably increased in width." The clinical diagnosis was *cutis verticis gyrata*, *acromegaly* and mechanical ptosis. The patient's eyes were operated on, and two large pieces of conjunctiva and tarsus of the upper lids were removed. The report of the histologic examination was as follows: "Chronic conjunctivitis with marked proliferation of palpebral conjunctiva with formation of glands. Many of the glands were distended with concretions. The tarsus was practically free from infiltration." The result of the operation was satisfactory, and the patient has remained comfortable since. Sisson reported that six roentgen ray treatments which the patient received improved the oily condition of the skin. After his discharge from the hospital the patient remained essentially well; he did not notice any decrease in the power or skill of his hands or feet or any increase in their size. No pain was felt over any bone or joint.

In 1923 he had had a herniotomy performed. In 1939 he entered the Boston Dispensary for treatment of a primary penile sore associated with positive results of a dark field examination and serologic tests. The extreme disfiguration of his skin and extremities was again noted. Of significance is the fact that the presence of leprosy was suspected on the patient's first examination in the dermatologic department.

On physical examination in 1939 the patient was middle aged, without kyphosis, well built and of normal height (168 cm.) and weight (75 Kg.).

The skin was slightly pigmented but otherwise was normal in color. The skin over the forehead and face down to the chin was appreciably thickened and covered by numerous fine openings representing sebaceous glands. Fatty material could be squeezed out from some of these openings. There was no edema, but the skin had a somewhat doughy consistency on palpation.

26. Sisson, R.: *Cutis Verticis Gyrata*, J. A. M. A. **86**:1126 (April 10) 1926.

The skin over the forehead (fig. 1) showed the striking furrowing which gives all patients with this condition such a characteristic angry appearance. The folds were firmer, more numerous and deeper than normal and could not be stretched out fully by muscular action. The frontal region was crossed by four horizontal lines, the lowest broken in the supranasal region by three small vertical furrows. The nasolabial fold was deeper than normal. A similar fold was formed just lateral to each corner of the mouth. The scalp was covered by thick, black hair, through which several parallel folds, running in somewhat sagittal direction, were palpable. These folds, which were firmer than those over the face, could not be stretched at all.



Fig. 1.—Face of the patient at the age of 43.

The skin over the feet up to the ankles and over the hands up to the wrists was slightly thickened (fig. 2). The normal lines over the palm and on the sides of the fingers and hands were deepened and ran farther down than normal (fig. 3). There were numerous fine folds, normally invisible, on the hands and fingers (microgyri, Naumann¹⁶).

The mucous membranes appeared normal, though slightly pale.

The eyelids, which were greatly thickened, were inflamed along their free margin; on closing, the upper one overlapped the lower by approximately 0.5 cm. The gap between the open lids was small (0.25 to 0.5 cm.). A fine, almost invisible scar was present above each upper lid.

The nose was large, with widened nares. There was no enlargement of the mouth or ears. The jaw was not prominent, while the closure and position of the teeth were normal. The tongue was normal in size.

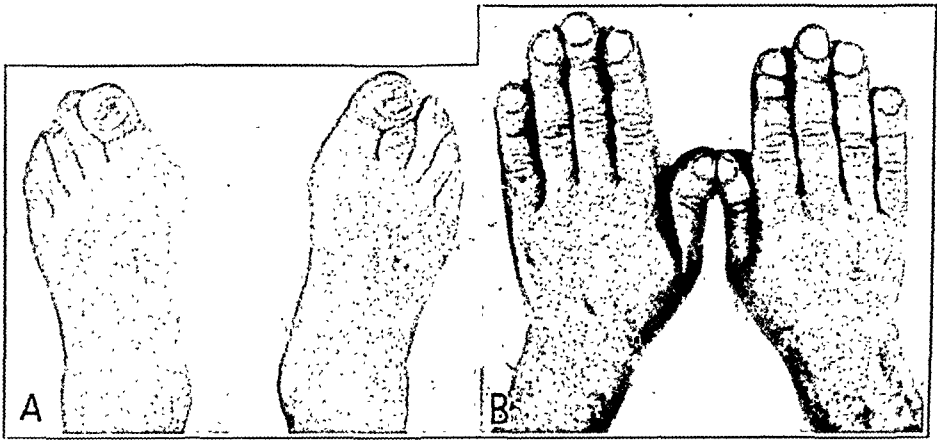


Fig. 2.—*A*, feet of the patient, showing extreme clubbing of the toes. *B*, hands of the patient, dorsal aspect.

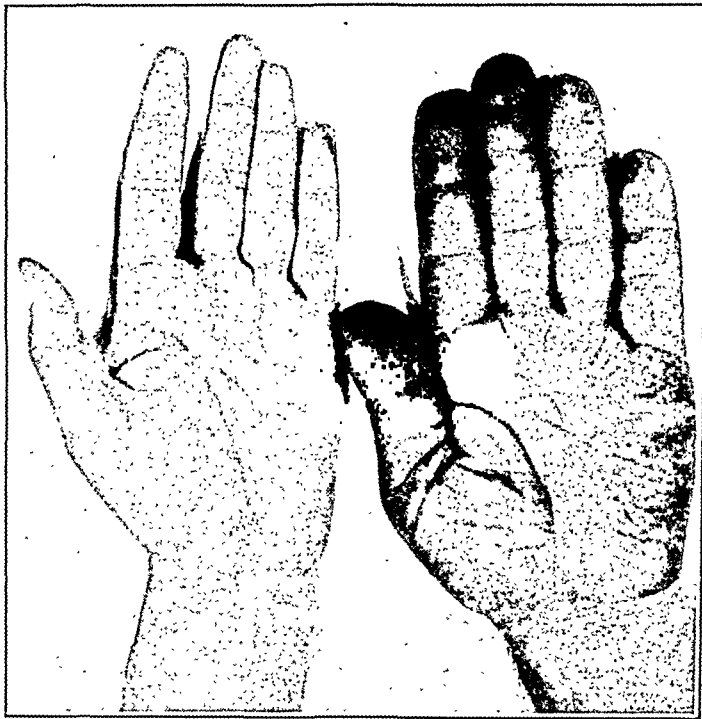


Fig. 3.—Hand of the patient compared with a hand of a normal person, palmar aspect.

Examination of the chest and of the abdomen revealed nothing of significance, except a slight but definite enlargement of the liver and spleen. Both organs later decreased in size and were not palpable at the patient's last examination, in 1940.

In table 1 the measurements of the extremities of this patient are compared with those of Wilhelm Hagner, who was studied by Erb. In the case of the former, the increase in length was insignificant as compared with that in circumference. Slight hypertrophy was found over the ankle and wrist as well.

TABLE 1.—*Comparison of Measurements of Erb's Patient and My Patient*

	Erb Right Side, Cm.	Brugsch Right Side, Cm.	Erb Left Side, Cm.	Brugsch Left Side, Cm.
Circumference of wrist.....	22.5	18.0	21.5	17.5
Length of whole hand from the volar fold.....	18.0	19.0	19.0	19.5
Length of thumb.....	7.0	8.2	8.2
Length of middle finger.....	12.0	10.5	10.5
Length of second finger.....	10.5	10.5	10.5
Width of middle hand without thumb.....	9.0	10.5	9.0
Width of middle hand between the styloid process of the ulna and the radius.....	7.0	7.0	7.0
Width of ulna.....	5.0	7.0	4.5
Width of thumb (end phalanx).....	3.5	3.5	3.5
Circumference of thumb.....	8.0	10.5	8.0
Width of thumb nail.....	2.5	3.5	2.7
Length of thumb nail.....	1.5	1.3
Width of middle finger.....	2.3	3.5	2.2
Circumference of middle finger (third phalanx)....	7.5	9.2	7.5
Circumference of middle finger (end phalanx)....	Appears thicker	7.0	7.8	7.0
Circumference of middle finger nail.....	2.0	2.5	1.0
Circumference of thigh, middle of femur.....	36.0	48.0	36.0	47.5
Circumference of knee.....	38.0	40.0	37.2	40.0
Circumference of lower part of leg.....	32.7	38.0	32.5	38.0
Circumference of ankle.....	31.5	31.0	32.0	30.5
Length of whole foot.....	27.5	25.0	27.0	25.0
Width of sole.....	11.0	10.0	11.0	10.0
Length of fibula.....	38.0	32.0	38.0	31.5
Length of big toe.....	7.5	9.5	9.0
Length of second toe.....	6.0	6.5	6.0
Width of big toe.....	4.0	4.0	4.0
Width of second toe.....	2.7	2.2	2.3
Circumference of big toe (end phalanx).....	12.0	11.2	11.5	10.5
Width of nail of big toe.....	4.5	2.5	4.5	2.3

TABLE 2.—*Comparison of Measurements* of Metacarpal and Metatarsal Bones in Renander's Patients, My Patient and a Normal Person*

		I		II		III		IV		V	
		L.†	B.†	L.	B.	L.	B.	L.	B.	L.	B.
Metacarpal....	Normal.....	46	11	69	10	67	10	69.5	8.5	50	9
	Renander's patient 1.	49	15	70	14	68	13	60.0	12.0	56	14
	Renander's patient 2.	49	14	72	12	70	12	60.0	11.0	58	10
	My patient.....	49	12	63	10	63	10	60.0	10.0	50	9
Metatarsal....	Normal.....	62	14	73	9	72	8	63	8	71	8
	Renander's patient 1.	65	21	73	11	73	10	74	12	72	12
	Renander's patient 2.	65	21	75	11	73	11	75	11	75	12
	My patient.....	63	20	59	11	65	11	62	8	70	9

* These measurements are based on roentgenograms. † L., length. ‡ B., breadth.

The nails, which were enlarged in all directions, had the "watch glass" appearance characteristic of clubbing. They were slightly livid. Toes and fingers showed extreme degrees of clubbing.

The bones of the skull and face had normal configuration; the lower jaw, in particular, was not enlarged or prognathic. Slight thickening and irregularity could be felt over the lower end of the radiuses and tibias. No tenderness was noticeable over any bone.

The joints were freely movable and were not swollen. They were normal in contour.

Roentgen examination revealed an extreme thickening of the cortex of both tibias, with irregular periosteal thickening. The same type of change was present in the forearm. The hands showed distinct squaring of the phalanges, with the

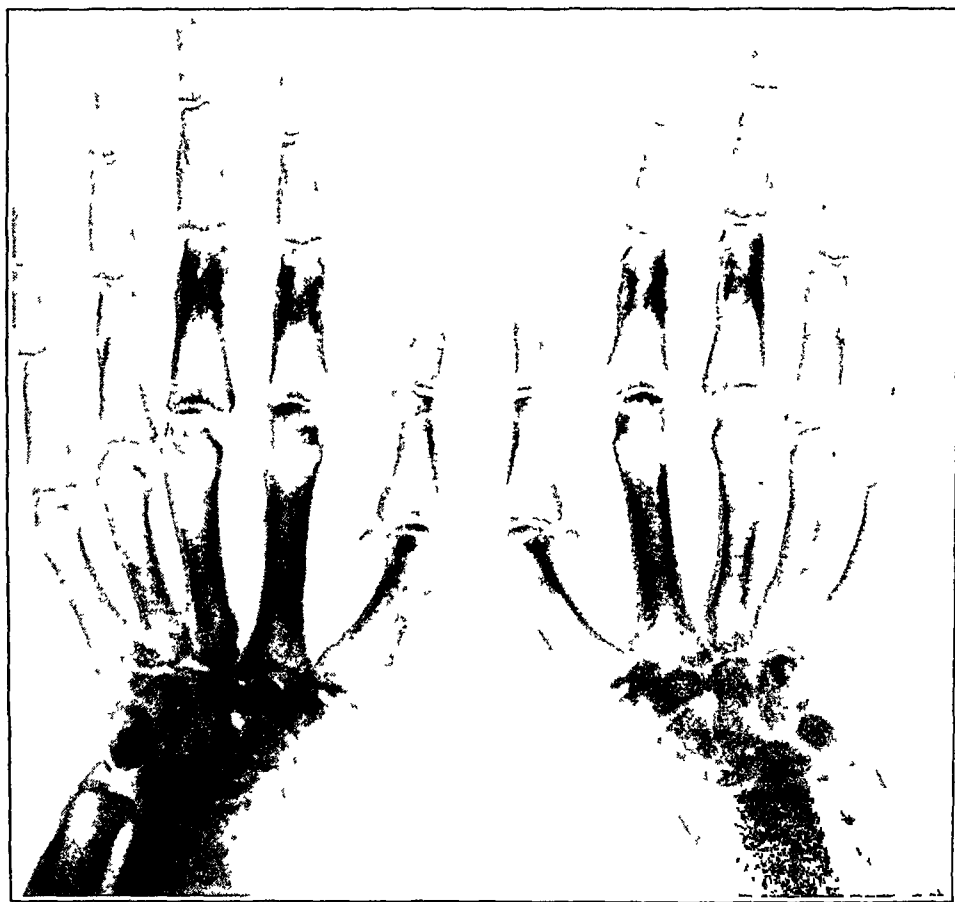


Fig. 4.—Roentgenogram of patient's hands.

exception of the terminal ones. There was a thickening of the cortex. The soft tissue around the end phalanges was also considerably thickened (fig. 4).

In table 2 the measurements of M. C.'s metacarpal and metatarsal bones are compared with measurements of those bones recorded for 2 of Renander's patients and for a normal person. In all cases the thickening over the metatarsal bones was more pronounced than that over the metacarpal bones.

Roentgen examination of the spine did not reveal any evidence of changes in bones. The lateral part of the skull was normal in thickness, and there were no erosions or abnormal calcifications. The convolutional markings were not increased. The sella turcica was normal in size and shape (greatest diameter 9 mm.).

COMMENT

The findings just mentioned can be included in the syndrome of acropachyderma with pachyperiostitis, which has received little attention in the United States. Its main features are cutis verticis gyrata, clubbing of the fingers and toes, squaring of the extremities and periosteal and cortical hypertrophy of the long bones. The face of a patient with the syndrome resembles that of a leper, while his legs and arms are similar to those of a person with the syndrome of pulmonary osteoarthropathy, described by Marie.

A study of the etiologic and symptomatologic relations of the syndrome of acropachyderma, together with a bibliography (somewhat incomplete), was published by Touraine, Solente and Golé.^{25b} Here I should like to stress certain new aspects of this condition.

Hereditry.—The familial occurrence of this syndrome was not recognized by Touraine, Solente and Golé. Although Renander mentioned familial occurrence, he still expressed the opinion that this condition represents a modified form of acromegaly.

The occurrence of this syndrome in two, and even three, members of one family was reported, as follows:

1. The first and most carefully studied family was that of Wilhelm and Karl Hagner, which has been mentioned. Karl, when last seen, at the age of 42, was well, free from any discomfort and able to work. Progression of the disease was slight after the age of 25. The autopsy report on Wilhelm, together with the photographs published by Virchow²⁷ and by Erb, clearly shows that his disease belonged to the syndrome under discussion and not to that of acromegaly or of osteoarthropathy. Although the photographs show that both brothers had a furrowing of the forehead, this fact was not discussed by Erb or by Friedrich. Arnold, however, briefly mentioned hypertrophy of the eyelids.

2. Leva²⁷ examined two cousins of whom the father of one and the mother of the second had a common great-grandfather. At the age of 22 and 23 respectively each noticed gradual enlargement of the hands and feet, together with formation of deep furrows over the forehead, neck and scalp. One of them suffered from sinusitis and visual disturbance (not due to involvement of the optic nerve). Roentgen examination showed enlargement of the sella turcica; therefore, the diagnosis of acromegaly was made. The patient was operated on and died from postoperative septicemia. On autopsy the sella turcica was found to be small and the hypophysis not enlarged. Microscopic examination revealed an increase of eosinophils in the anterior lobe of the hypophysis

27. Virchow, R.: *Illust. M. News* 2:241, 1889.

but no adenoma or other tumor. His cousin remained perfectly well, and Adrian²⁸ reported that his condition four years later was stationary.

3. Sicard and Haguénau¹⁸ observed a 41 year old patient who first noticed enlargement of his hands at the age of 18. Two years later his feet became involved but less severely. He also noticed heaviness over the upper lids and a decrease in the palpebral fissures as the result of progressive hypertrophy of both upper and lower tarsal cartilages. Finally the fissures of the eyes became so small that resection of parts of the upper lids became necessary. His visual ability afterward was good. There was no sign of gigantism, kyphosis, prognathism or macroglossia. His nose showed some enlargement. The appearance of the skin over the forehead was not mentioned. The appearance of the hands was more like that observed in cases of osteoarthropathy. Roentgenograms of the long bones were not significant. He died in good health at the age of 58, from an accident. No autopsy was reported.

Because the roentgen examination showed enlargement of the sella and "destruction" of the clinoid processes, the authors chose the name *acroméganisme partiel familial (type digitopalpebral)*.

One of the patient's brothers at the age of 18 also noticed the beginning of the same changes involving the hands, feet and palpebrae.

4. Oehme¹⁹ studied three brothers all suffering from similar swelling of the legs and arms in addition to furrowing of the skin over the forehead and scalp. Careful roentgen examination of the bones revealed, for the first time in vivo, the presence of periosteal new formation—thickening of the corticals of several long bones and squaring of the metapalangeal bones. The first symptoms of abnormal growth (pain and discomfort) developed in the brothers at the age of 14 or 15. One sister, who was not observed, was said to have exhibited the same changes. Growth of hair over the face was retarded in all 3 patients. Careful search did not reveal any other major pathologic condition.

5. Müller²⁹ saw two brothers with this disorder. At the age of 17 one brother noticed swelling of one knee joint, which necessitated prolonged rest in bed. During the following years he also noticed an increase in the size of his hands and feet. Müller did not mention the skin of the face, which, according to the photographs published, showed typical furrowing.

Similar changes, but with more pronounced involvement of the knees, were found in the other brother. There were also other findings typical of acropachyderma with pachyperiostitis, such as furrowing of the skin and clubbing. Both knees were full of fluid. An arthrotomy

28. Adrian, C.: Dermat. Centralbl. **19**:2 and 34, 1916.

29. Müller, W.: Beitr. z. klin. Chir. **150**:616, 1930.

which was performed showed extreme synovial thickening with numerous villous projections. Cultures of fluid were sterile, and on histologic examination chronic inflammatory changes were seen. Roentgenograms of the sella showed a rather large diameter (15 mm.) but no other abnormality. No signs or symptoms of acromegaly were present. Roentgen examination of the extremities revealed advanced periostitis.

Thus, in five families several male members were affected by a similar abnormality of growth.

Age.—All patients noticed the beginning of abnormal growth after the age of 14. It ceased to increase noticeably after they reached an age of 22 to 25.

Duration.—All patients, except 2, lived their normal span of life. Wilhelm Hagner died from bronchiectasis, and Leva's patient died after a transnasal operation. A third died at the age of 58 from an accident.

Sex.—In none of the 30 to 40 cases reported in the literature was the patient a woman. Oehme mentioned a similar overgrowth in a sister of his 3 patients but never saw the girl.

Race.—Reports from France, Germany, Italy, Great Britain, Sweden, Canada (Roy³⁰), Japan (Ota¹⁵) and the United States indicate that there is no definite relation to certain races. I was impressed, however, as others^{25b} have been, by the uniformity in appearance and color of hair (black, thick and abundant), the medium size and the similarity in facial expression in all patients. These characteristics are evident from photographs in the publications of Renander, Solente and associates, Naumann, Ota, and Bussalai.

Skin.—The folds over the forehead and scalp are firm and not comparable to those formed by loss of connective tissue and widening of the skin, a condition occasionally found in imbeciles or in patients with acromegaly (so-called "bulldog" head of Cushing). In cases of acropachyderma histologic examination of the skin reveals hypertrophy of certain parts, mainly the corium, sweat glands and oil glands. These glands show a remarkable widening and tortuosity (Bussalai, Groenberg). They are apparently easily subject to secondary infection or to invasion by parasites (Ota, Groenberg).

The face appears fatty and is covered by fine black spots caused by enlargement of sebaceous glands. Sometimes droplets of fat can be squeezed out.

Diminished growth of hair over the axilla and face is common but is not found in all patients. (Both Hagner brothers had abundant beards.)

30. Roy, J.: Presse méd. 45:403, 1937.

Eyelids.—My patient, the Hagner brothers and the patients of Sicard, Rintelen³¹ and Roy develop a disfiguring enlargement of the eyelids. In some instances the resulting visual impairment warranted resection of conjunctivas and cartilage. Sicard, Rintelen and Sisson operated on their patients and obtained good results. Studies of the excised parts (Sisson, Rintelen) showed enlargement of the skin, as well as widening and enlargement of the meibomian glands, without major inflammatory changes.

Extremities.—There is a striking similarity between the appearance of the hands and feet in cases of this disease and that observed in cases of pulmonary osteoarthropathy. In advanced forms of osteoarthropathy there may be a periosteal enlargement of the distal portion of long bones, e. g., the radius, ulna and tibia. However, the presence of these lesions in patients without any underlying disease and in combination with furrowing of the face is of diagnostic importance. The grotesque and elephantiasic thickening of ankles and wrists observed in some patients with acropachyderma has not been found in those with pulmonary osteoarthropathy. In acromegaly the normal form of fingers and toes, although enlarged in all dimensions, is preserved. While hypertrophy of the bones and internal organs is uniform, clubbing is absent.

Roentgen Study.—Extensive use of roentgen ray examination has shown that there is a much wider involvement of the skeletal bones than had originally been suspected. The following are the most noticeable changes:

1. Periosteal enlargement and apposition is strongest in the diaphysis of the metatarsal and the metacarpal bones and leads to a "bottle-like" deformity. The spine, clavicles and patellas are occasionally covered by such periosteal bone formation. The amount of periosteal new formation may vary from small irregular particles to confluent masses (like that in Wilhelm Hagner). The terminal phalanges, however, are always spared. Despite lack of visible changes, the condition in my patient, on roentgen examination, has shown progression during the last twenty years.

2. The corticalis appears extremely thickened, especially over the diaphysis. Here eburnation may lead almost to obliteration of the central cavity. In my patient the corticalis measured up to 10 mm. over the diaphysis of the tibia.

3. With 3 exceptions, already discussed (Leva, Sicard and Müller), the sella turcica and other parts of the skull were perfectly normal in size and structure. Enlarged sinuses were seen once. None of the patients exhibited enlargement or prognathia of the jaw.

31. Rintelen, F.: Ztschr. f. Augenh. 92:1, 1937.

Endocrine Organs.—In contrast to those with acromegaly most of the patients asked were sexually potent. My patient acquired syphilis at the age of 40, more than twenty years after the beginning of the acropachyderma. Naumann's patient had a positive reaction to serologic tests. Several other patients were married. However, all remained childless. The relation of this disease to such features as sex, age and bone growth makes the dysfunction of an endocrine gland most likely. Should further studies reveal that the hypophysis (anterior lobe) is responsible, the condition still has to be strictly separated from the eosinophilic adenoma causing acromegaly.

Physical examination, metabolic studies and numerous tests did not reveal involvement of any endocrine gland to such a degree that a glandular deficiency could be detected.

Laboratory Tests.—Studies of the blood—hemoglobin concentration, white and red cell counts, differential count, sedimentation and Wassermann reaction (which became positive in my case after the onset of syphilis)—have not yet revealed any consistent abnormality. Studies of calcium, phosphorus and phosphatase levels in the blood of my patient showed normal values. Oehme examined the spinal fluid for its content of hypophysial hormone, but was unable to detect deviations from normal; Groenberg found alimentary glycosuria after a dextrose tolerance test.

Tests for androsterone and gonadotropin in the urine of my patient gave negative results.

DIFFERENTIAL DIAGNOSIS

Acromegaly.—This syndrome has only two features in common with acromegaly, namely, overgrowth of the bones of the hands and feet and a marked tendency to sweating. In contrast to the changes in acromegaly, however, the bones of the hands and feet show partial hypertrophy and not enlargement *en long*, or hypertrophy of the whole bone. The enlargement of the skull and jaw so characteristic of acromegaly is missing. Roentgenograms of the hypophysis are normal in the majority of the reports. Absence of progression after the age of 25 (except perhaps some increase in periosteal overgrowth) is also of diagnostic value.

Pulmonary Osteoarthropathy.—This condition is apparently not an entity. It involves the soft tissues of the extremities (clubbing) and the long bones (periosteal reaction). It does not affect the end phalanges. There are thus definite similarities between both this and the aforementioned condition. In pulmonary osteoarthropathy, however, the periosteal overactivity is most evident near the epiphysis. Pain over the bones involved is frequent, and attacks of fever are often present. Furrowing of the face has never been observed. It must be

admitted, however, that the similarity of the changes in the bones forces one to consider the possibility of a common cause. The condition of patients with hereditary clubbing of the fingers and toes may turn out, on careful examination, to be pachyacria with pachyperiostosis.

Cutis Verticis Gyrata.—This gyrus-like thickening of the skin over the neck, forehead and scalp was first described in 1906 by Jadassohn; it occurs in different conditions. Fisher³² differentiated local cutis verticis gyrata which is the result of infections of nevi and of trauma from that found in combination with systemic diseases involving the bones, e. g. acromegaly and imbecility.

Leprosy.—This disease can be ruled out by a search for bacteria, a biopsy of the skin and consideration of the whole clinical picture. That difficulties arise in making a correct diagnosis is evident from such incidents as the one in which Groenberg's and Renander's patient was refused admission to the United States by the immigration authorities because he was suspected of having leprosy.

NAME

Touraine, Solente and Golé, who recognized that enlargement of the fingers and toes and furrowing of the skin over the forehead, with associated periostitis, are the outstanding features of this syndrome, suggested the name pachyderma with pachyperiostosis. I believe that the addition of "acro-" to "pachyderma" is justified in order to emphasize the predominant involvement of the hands and feet. The name acropachyderma with pachyperiostitis, therefore, seems the most comprehensive.

SUMMARY

The case of a patient with pachyderma and periostosis is reported. The uniformity of this syndrome affecting males after puberty and leading to extreme thickening of skin and bones is discussed. Its separation from other conditions is emphasized. The name acropachyderma with pachyperiostitis is suggested.

32. Fisher: Arch. f. Dermat. u. Syph. **141**:251, 1922.

ACACIA IN THE TREATMENT OF THE NEPHROTIC SYNDROME

INFLUENCE OF ACACIA, INJECTED INTRAVENOUSLY, ON CONCENTRATION
OF PROTEINS AND ON COLLOID OSMOTIC PRESSURE OF THE SERUM

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The intravenous administration of solution of acacia to patients with a nephrotic type of edema is being employed by many physicians. Two of us (Goudsmit and Binger¹) recently reviewed the literature on such treatment and reported experiences with this therapeutic adjunct in 40 cases, in 36 of which the patients were effectively and rapidly relieved of their edema. No harmful effects were noticed.

It has been tacitly assumed by most investigators that the colloid osmotic pressure of the serum is increased after the introduction into the blood stream of quantities of acacia such as were employed with favorable results. Indeed, Kerkhof² reported 1 case in which there was extensive nephrotic edema and the serum exerted a colloid osmotic pressure of 8 mm. of mercury (109 mm. of water). Three hundred grams of acacia in 30 per cent solution was given in the course of three days. One hour after the completion of the last injection the colloid osmotic pressure was 15 mm. of mercury (204 mm. of water), and three days later it still amounted to 12.6 mm. of mercury (171 mm. of water). Butt, Power and Keys,³ on the other hand, after one injection of 500 cc. of a 6 per cent

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At the time this work was done Dr. Goudsmit was a Fellow in Medicine of the Mayo Foundation.

1. Goudsmit, A., Jr., and Binger, M. W.: Acacia in the Treatment of Nephrotic Syndrome, *Arch. Int. Med.* **66**:1252-1281 (Dec.) 1940.

2. Kerkhof, A. C.: Plasma Colloid Osmotic Pressure as a Factor in Edema Formation and Edema Absorption, *Ann. Int. Med.* **11**:867-880 (Dec.) 1937.

3. Butt, H. R.; Power, M. H., and Keys, A.: The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, *J. Lab. & Clin. Med.* **24**:690-695 (April) 1939.

solution of acacia into a patient with cirrhosis of the liver found a temporary increase of the colloid osmotic pressure, but even a second injection, twenty-four hours later, could not effect its maintenance at the higher level. In another case, after a single injection there was a decrease of colloid osmotic pressure and even seven days later the original level had not been regained. Peters⁴ mentioned unpublished studies of Wies indicating that after intravenous injection of acacia "the colloid osmotic pressure may rise slightly, sometimes not at all above its previous level."

The changes observed in the concentration of serum proteins subsequent to the injection of solution of acacia are more consistent; either insignificant variations or frank decreases have been noted by various authors. The importance of these decreases, which can be observed in man and in animals, was stressed by Dick, Warweg and Andersch,⁶ Hall⁷ and Heckel, Erickson, Yuile and Knutti.⁸ Since the total colloid osmotic pressure after injection of solution of acacia is assumed to be due to the sum of the particles of protein and of acacia, significant decreases in the concentration of the serum proteins might well defeat the purpose of the administration of acacia.

After a demonstration that satisfactory therapeutic results can be obtained through the incorporation of injections of solutions of acacia into the regimen of the patient with nephrotic edema, it appeared essential to obtain a more comprehensive picture of the mechanism of its action. The present study thus is mainly concerned with observations on the changes of the concentration of the serum proteins and of the colloid osmotic pressure of the serum subsequent to the administration of solutions of acacia to patients with the nephrotic syndrome.

METHOD

A review of the patients treated, including criteria of diagnosis, has been published elsewhere.¹ For the purpose of this study a colloid osmotic pressure of the serum not exceeding 200 mm. of water was further added to the requirements of a diagnosis of the nephrotic syndrome. The preparation of acacia used represented the filtrate of an autoclaved solution containing 6 Gm. of acacia per hundred cubic centimeters of solution.

4. Peters, J. P.: *Body Water: The Exchange of Fluids in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

5. Footnote deleted by the authors.

6. Dick, M. W.; Warweg, E., and Andersch, M.: *Acacia in the Treatment of Nephrosis*, J. A. M. A. **105**:654-657 (Aug. 31) 1935.

7. Hall, W. K.: *Effects of Intravenous Injections of Acacia on Certain Functions of the Liver*, Proc. Soc. Exper. Biol. & Med. **38**:46-48 (Feb.) 1938.

8. Heckel, G. P.; Erickson, C. C.; Yuile, C. L., and Knutti, R. E.: *Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia*, J. Exper. Med. **67**:345-360 (March) 1938.

The colloid osmotic pressure was determined by a modification of the membrane bag arrangement of Starling⁹ as described by Butt, Power and Keys.³ Serum proteins were estimated from the value for protein nitrogen as determined by a modified Kjeldahl method, the factor 6.25 being used to convert nitrogen to protein. Acacia in the serum was analyzed according to the method of Power.³ Unless stated otherwise, determinations after administration of acacia always represent conditions at least twenty hours, and usually not more than seventy-two hours, after completion of a course of injections of solution of acacia.

RESULTS

Since measurements of colloid osmotic pressure in the arrangement used in this study have not been reported before in a series of cases of the nephrotic syndrome, it appeared essential to begin the description of the results with a short analysis of the relation of colloid osmotic pressure to serum proteins in 35 consecutive hospitalized patients with the nephrotic syndrome. This relation is represented in figure 1. As can be seen, the group includes 4 patients who did not show manifest edema at the time of their admission to the hospital. Their colloid osmotic pressures are obviously among the highest. Thus in this series a critical level of colloid osmotic pressure below which the untreated patient with the nephrotic syndrome has a manifest edema is apparent. Such a level would be close to 166 mm. of water.

Generally speaking, the colloid osmotic pressure becomes greater as the concentration of serum proteins increases. Variations are fairly large, but this is not surprising in view of the abnormal features of the serum proteins in the nephrotic syndrome, among which the deranged ratio of albumin to globulin, different from case to case, is the one most frequently studied. Nevertheless the general relation appears essentially linear. The colloid osmotic pressure appears to decrease within the range examined by approximately 60 mm. of water for a diminution of concentration of serum proteins of 1 Gm. per hundred cubic centimeters.

Definite changes in this relation between serum proteins and colloid osmotic pressure take place after a course of injections of solution of acacia ranging from 60 to 150 Gm. (fig. 2). It is as if all data were forcibly moved to the left. In other words, the apparent colloid osmotic pressure exerted per gram of protein is considerably increased. Or, assuming that the "specific" colloid osmotic pressure of the serum proteins has not changed appreciably through the administration of acacia, the acacia has added osmotically active particles to the serum.

On the basis of the latter assumption, we have examined the data concerning 22 patients for whom determinations of serum proteins, colloid osmotic pressure and serum acacia, both before and after the injection of solution of acacia, had been performed. In this group no

9. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19**:312-326, 1896.

restrictions have been placed on the time limit after the administration of acacia. The colloid osmotic pressure which might be tentatively assigned to the acacia in any given instance was arrived at by applying

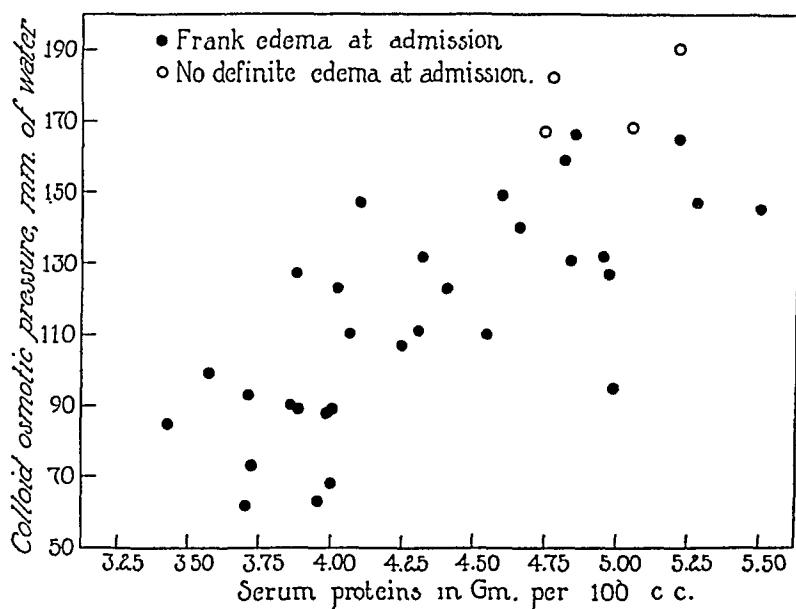


Fig. 1.—Relation of the colloid osmotic pressure to the concentration of the serum proteins in 35 cases of the nephrotic syndrome.

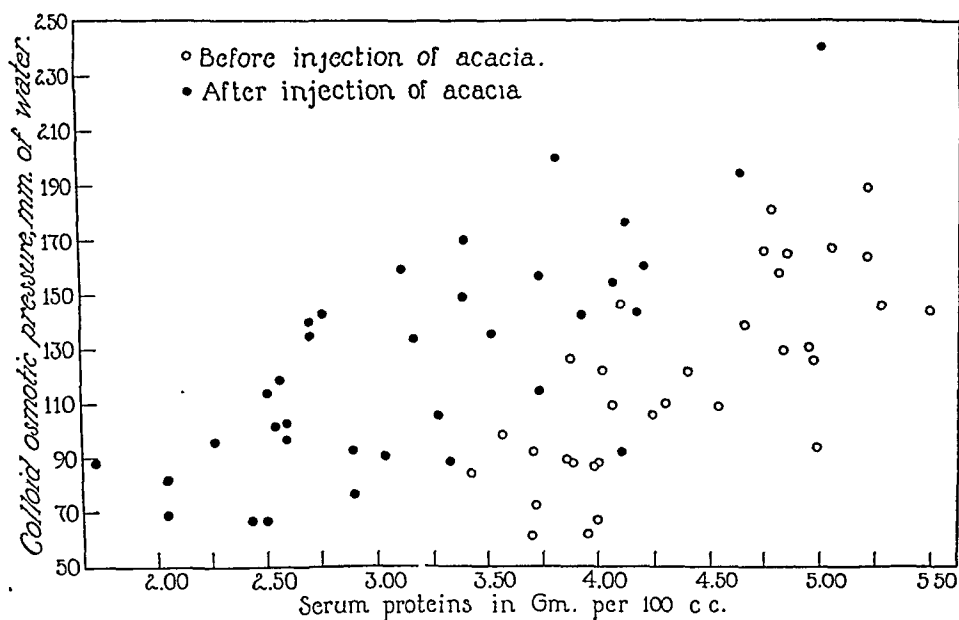


Fig. 2.—Relation of colloid osmotic pressure to concentration of serum proteins as modified by the presence of acacia.

a correction for the differences in protein content before and after the administration of acacia on the basis of a difference of colloid osmotic pressure of 60 mm. of water for a difference in serum protein concentra-

tion of 1 Gm. per hundred cubic centimeters. An actual example of such a calculation is demonstrated in table 1.

The resultant values for the colloid osmotic pressure assigned to the acacia present in the serum were subsequently studied in their relation to the actual concentration of acacia (fig. 3). A casual inspection shows that in general the greater colloid osmotic pressures were due to the greater concentrations of acacia. The figures, in addition, were subjected to a closer analysis, as follows: Of the 22 observations, 11 were obtained at a concentration of acacia in the serum of less than 1,650 mg. per hundred cubic centimeters and an equal number at concentrations higher than that. In the group with the lower concentrations of acacia an average "acacia" osmotic pressure of 55 mm. at an average concentration of

TABLE 1.—*Example of Calculation of the Fraction of the Colloid Osmotic Pressure of the Serum Presumably Due to the Presence of Acacia*

Date	Colloid Osmotic Pressure, Mm. Water	Serum Proteins, Gm. Per 100 Cc.	Acacia, Mg. per 100 Cc.	Comment
12/20/37	89	4.01	0	
12/27/37	93	2.91	1,500	A total of 90 Gm. of acacia administered to patient in divided doses on 12/20, 12/21 and 12/24
Calculation:				
Total gross gain in colloid osmotic pressure.....				4 mm.
Decrease of serum proteins, 4.01 — 2.91 = 1.10. This represents a calculated loss of colloid osmotic pressure of 1.10 × 60 =.....				66 mm.
Net colloid osmotic pressure, due to acacia, 1,500 mg. per hundred cubic centimeters.....				70 mm.

acacia of 1,161 mg. per hundred cubic centimeters was obtained. For the group this would correspond to an average value of $\frac{55}{1.161} = 47$ mm. of water pressure for 1,000 mg. of acacia per hundred cubic centimeters (1 per cent). In the group with the higher concentration of acacia, an average "acacia" osmotic pressure of 90.5 mm. at an average concentration of acacia of 2,009 mg. per hundred cubic centimeters was obtained. Thus for this group an average colloid osmotic pressure might be assigned of $\frac{90.5}{2.009} = 45$ mm. of water per 1,000 mg. of acacia per hundred cubic centimeters. If a line is drawn through the origin of the coordinates (fig. 3) and through a point representing the mean colloid osmotic pressure (72.3 mm. of water) at the mean concentration of acacia (1,585 mg. of acacia per hundred cubic centimeters of serum), it is found that fully one half of the observations are at a distance of not more than 6 mm. of pressure of water from this line. In view of the close proximity of the figures in the groups with the higher and lower concentrations of acacia

the conclusion appears justified that the presence of acacia in the serum raises the colloid osmotic pressure in proportion to its concentration, namely, about 46 mm. for a concentration of 1 per cent. This value corresponds closely to the one directly determined on fresh solutions of acacia by Saslow,¹⁰ who found an average pressure of 260 mm. of water for a 6 per cent solution of acacia in a 0.9 per cent solution of sodium chloride, and to one determined by Wies and Peters,^{10a} who found it to be 252 mm. of water. These figures would correspond to $\frac{260}{6} = 43$ mm. and $\frac{252}{6} = 42$ mm., respectively, for a concentration of 1 per cent of acacia.

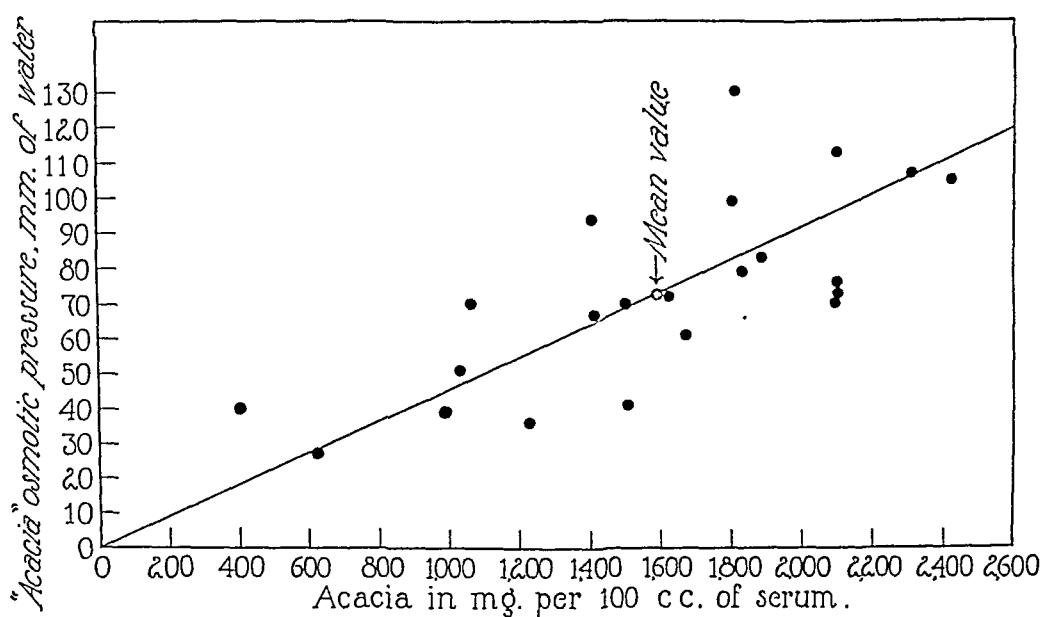


Fig. 3.—Osmotic pressure due to acacia as a function of its concentration in the serum. A line has been drawn through the origin of the coordinates and through the value for mean colloid osmotic pressure at the mean concentration of acacia.

Changes in the concentration of serum proteins of the patients after solutions of acacia were injected varied between + 7 and — 44 per cent of the original concentration. The average in 27 instances was — 22 per cent, 16 of the changes ranging between — 12 and — 32 per cent. The influence of the amount of acacia administered on the percentage decrease of serum proteins appears insignificant (table 2). Neither could a corre-

10. Saslow, G.: Osmotic Pressure of Gum Acacia Solutions, *Proc. Soc. Exper. Biol. & Med.* **40**:277-281 (Feb.) 1939.

10a. Wies, C. H., and Peters, J. P.: The Osmotic Pressure of Proteins in Whole Serum, *J. Clin. Investigation* **16**:93-102 (Jan.) 1937.

lation be established between the concentration of acacia in the blood reached as a result of the administration of acacia and the percentage of decrease in concentration of serum proteins.¹¹ Nor did the concentration of serum proteins before the administration of acacia have any relation to its subsequent relative decrease, the average percentage decrease being essentially the same in the group with a relatively high initial concentration of serum proteins (more than 4.06 Gm. per hundred cubic centimeters) and in the group with the lowest initial concentration of serum proteins (4.06 Gm. or less per hundred cubic centimeters). The absolute decrease, however, appears roughly proportional to the initial concentration.

TABLE 2.—*Changes in the Concentration of the Serum Proteins Following a Course of Injections of Acacia in Patients with the Nephrotic Syndrome*

		Concentration of Serum Protein					Amount of Acacia Admin- istered (Average), Gm.
		Number of Patients	Before Acacia (Average), Gm. per 100 Cc.	Change After Acacia			
				Average			
				Range, Percentage	Per- centage	Gm. per 100 Cc.	
Amount of acacia administered, Gm.	90 or less.....	16	4.35	+3 to -43	-21	0.94	84
	More than 90...	11	3.86	+7 to -44	-24	0.99	117
Original concentration of serum proteins, Gm. per 100 Cc.	4.06 or less.....	15	3.58	+7 to -37	-21	0.83	103
	More than 4.06.	12	4.86	-1 to -44	-23	1.14	91
Total.....		27	4.14	+7 to -44	-22	0.96	97

From the point of view of the hydrodynamic aspects of nephrotic edema, a direct comparison between the colloid osmotic pressure before and after the administration of acacia appears extremely important. Thus in figure 4, the colloid osmotic pressure before the administration of acacia is plotted on the abscissa and the colloid osmotic pressure not later than three days after the completion of the series of injections is plotted

11. In the present series no satisfactory correlation could be established between the magnitude of the total therapeutic dose of acacia administered (which varied, in different cases, between 60 and 150 Gm.) and the subsequent concentration of acacia in the serum. Of course, in the individual case the latter increases as additional acacia is administered. But, apparently, the interindividual variability of the relation between dose and concentration overshadows the correlation in the individual case.

on the ordinate. An unchanged colloid osmotic pressure is represented by a point on the diagonal line which passes through the origin of the coordinates and makes an angle of 45 degrees with the horizontal. We have allowed an extra range of pressure of 15 mm. of water for changes to which probably no definite significance can be attributed and have called all observations within this zone unchanged. Above the upper slanting line are all cases in which the colloid osmotic pressure was increased, and below the lower slanting line all those in which the pressure was decreased.

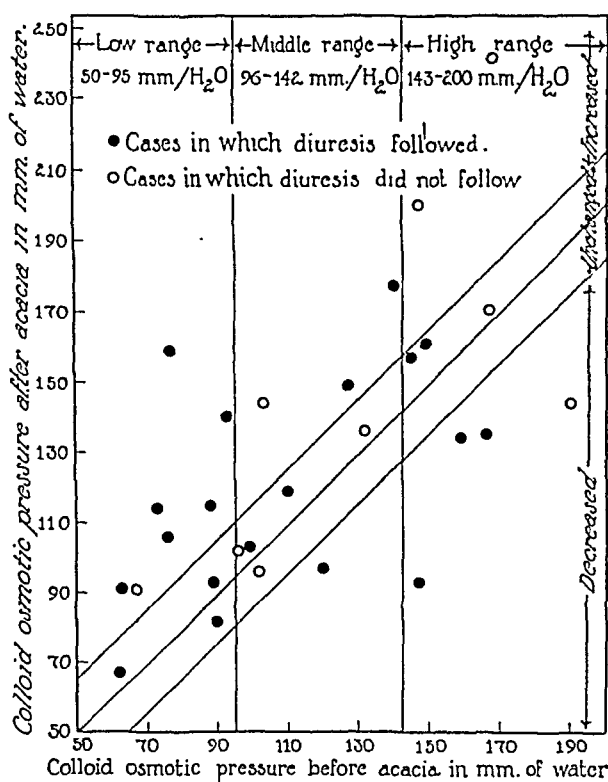


Fig. 4.—Influence of injections of acacia on the colloid osmotic pressure of the serum.

For purposes of closer study, we have divided the range of the original colloid osmotic pressures into three subdivisions (table 3). In the group with the lowest original colloid osmotic pressures, increases after the administration of acacia are observed with the greatest frequency and frank decreases are absent. On the other hand, in the group with the high initial colloid osmotic pressures, decreases outnumber increases two to one. The middle range, when analyzed for its changes in colloid

osmotic pressure, appears to represent a phase definitely intermediate between the two extremes.

Of the 28 patients studied, administration of acacia was promptly followed by disappearance of edema in 20. Three patients with edema failed to respond with diuresis, and in 5 patients no edema was present at the time the injections of solution of acacia were begun. Statistical analysis of the data reveals a lack of correlation between diuretic response (or its absence) and changes of colloid osmotic pressure. This absence of correlation is well illustrated by the fact that in 4 instances in which a frank decrease of colloid osmotic pressure was observed the diuretic response was just as satisfactory as in 9 cases in which the colloid osmotic pressure was definitely increased.

TABLE 3.—*Changes of the Colloid Osmotic Pressure of the Serum Following a Course of Injections of Acacia in Patients with the Nephrotic Syndrome*

Colloid Osmotic Pressure Before Acacia, Mm. Water	Colloid Osmotic Pressure After Acacia						Total	
	Increased		Unchanged		Decreased			
	Number	Per- centage	Number	Per- centage	Number	Per- centage	Number	Per- centage
50-95 (low range)	7	70	3	30	0	0	10	100
96-142 (middle range)	3	33	5	56	1	11	9	100
143-200 (high range)	2	22	3	33	4	44	9	100
Total.....	12	43	11	39	5	18	28	100

COMMENT

Lepore¹² studied the influence of acacia on plasma (serum) proteins, hematocrit reading and plasma volume in patients with a nephrotic type of edema. Blood volume and plasma volume are essentially normal in this syndrome.¹³ After an injection of solution of acacia, plasma protein and hematocrit values decrease and circulating plasma volume increases.¹⁴

12. Lepore, M. J.: Acacia Therapy in Nephrotic Edema, *Ann. Int. Med.* **11**: 285-296 (Aug.) 1937.

13. After completion of the manuscript of this paper, a detailed study by Harris and Gibson (Clinical Studies of Blood Volume: Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, *J. Clin. Investigation* **18**:527-536 [Sept.] 1939) of the volume of the blood in case of Bright's disease was published. Their extensive data appear well in harmony with our statement.

14. This increase in plasma volume has been known since the work of Bayliss (Intravenous Injection in Wound Shock, London, Longmans, Green & Company, 1918) and was utilized by Keith (Traumatic Toxemia as a Factor in Shock,

Thus it appears that most, if not all, of the decreases in plasma protein concentration noted might well be due to dilution. In our cases, the decrease of 22 per cent in serum protein concentration could be well explained by an increase of circulating plasma (serum) volume of 28 per cent. In actual figures, this would amount to an increase of volume of less than 1 liter, and changes of that order of magnitude have frequently been observed by Lepore.¹² In our experience the concentration of hemoglobin in the blood is decreased in essentially corresponding amounts, and even in those instances in which the greatest decrease of serum proteins was observed (up to 44 per cent) the calculated corresponding increase in blood volume was not greatly outside the range of the actual volume of acacia solution administered.

The view that dilution is largely responsible for these decreases of concentration of the serum proteins is supported by results of experiments performed by two of us (Goudsmit and Power) and Bollman.¹⁵ After the injection of solution of acacia into healthy dogs it was found that the changes of the hematocrit value pointed to essentially the same values for the increase of plasma volume as did the changes of the concentration of the plasma proteins. A similar general parallel between changes of hematocrit reading and of plasma protein concentration is evident from the data of Heckel and his co-workers.⁸

The changes in colloid osmotic pressure resulting from the injection of solution of acacia appear to be directly related to the resultant concentration of acacia in the serum and the decrease in serum proteins. Figure 3 shows that by assigning a specific colloid osmotic pressure of 60 mm. of water for 1 per cent difference in serum protein concentration and 48 mm. of water for 1 per cent difference in acacia concentration a reasonably fair prediction of the actual changes of colloid osmotic pressure can be made.

In the group with the lowest initial colloid osmotic pressure (fig. 1), generally speaking, the lowest initial concentrations of serum proteins are found. Their relative decrease is independent of either the size of the dose of acacia or the initial protein concentration. The absolute value of the decrease, however, is lowest in the group with the lowest initial concentration of proteins, in other words, in the group with the lowest initial

Medical Research Committee, Special Report Series, no. 26, London, His Majesty's Stationery Office, 1919, pp. 36-44; Blood Volume Changes in Wound Shock and Primary Haemorrhage, Medical Research Committee, Special Report Series, no. 27, London, His Majesty's Stationery Office, 1919, pp. 2-16) and others in the treatment of shock (see general review by Amberson, W. R., Blood Substitutes, *Biol. Rev. Cambridge Phil. Soc.* **12**:48-86 [April] 1937).

15. Goudsmit, A., Jr.; Power, M. H., and Bollman, J. L.: Some Effects of the Injection of Acacia with Special Reference to Renal Function, *Proc. Soc. Exper. Biol. & Med.* **47**:254-257 (June) 1941.

colloid osmotic pressure. Since the final concentration of acacia is essentially the same in each group, the finding of the greatest number of increases of colloid osmotic pressure in the group with the lowest initial pressures is readily understood.

The response of the colloid osmotic pressure for a group of patients thus appears directly related to their distribution of initial colloid osmotic pressures. Clinical success or the lack of it, on the other hand, appears essentially unrelated to the changes of colloid osmotic pressure as observed in this study. Thus a method of treatment advocated because of certain theoretic considerations, namely, to increase colloid osmotic pressure, proves effective, even though on subsequent analysis the mechanism involved appears open to reconsideration.

Van Slyke ¹⁶ once remarked, "There is . . . to be considered the fact that fluid can leave the blood by two paths, either into the tissue spaces and lymph channels, or through the kidney into the urine." In the discussions of the mechanism underlying the development of a nephrotic (hypoproteinemic) type of edema investigators might well have over-emphasized the pathway of fluid into the tissue spaces and lost sight of its equally important alternative, namely, the pathway through the kidney. Recent experiments on healthy dogs by Bollman and two of us (Goudsmit and Power ¹⁵) indicate that after intravenous injection of acacia in an isotonic solution of dextrose a considerable increase in the rate of excretion of chloride is regularly encountered, even though the concentration of chlorides in the blood is usually decreased as a consequence of this procedure. Renal function otherwise remains essentially undisturbed. Studies of excretion of chloride in human beings suffering from a nephrotic type of edema under treatment with acacia have been conducted since. The results, reported elsewhere, appear to substantiate the importance of a renal factor in the mechanism of action of acacia.

SUMMARY AND CONCLUSIONS

In 28 patients with the nephrotic syndrome who were treated with acacia the following observations were made:

1. The concentration of acacia in the serum resulting from the injection of 60 to 150 Gm. ranged between 1,000 and 2,500 mg. per hundred cubic centimeters.
2. The concentration of serum proteins usually diminished. As an average this amounted to 22 per cent of the original concentration. This related decrease could not be correlated with the amount of acacia administered, with the resultant concentration of acacia in the serum or with

16. Van Slyke, D. D.: *Factors Affecting the Distribution of Electrolytes, Water and Gases in the Animal Body*, Philadelphia, J. B. Lippincott Company, 1926.

the initial concentration of serum proteins. Increases in circulating plasma volume and concomitant dilution of its constituents appear to account adequately for the decrease of serum proteins.

3. The gross changes in colloid osmotic pressure subsequent to injections of solution of acacia are directly related to the absolute changes of the concentration of the serum proteins and of the concentration of acacia. If certain values are assigned for the "specific" osmotic pressures of serum proteins and of acacia, the changes of colloid osmotic pressure can be predicted fairly accurately. In approximately half of the patients the calculated changes were within 6 mm. of the observed values.

4. The colloid osmotic pressure of the serum may be increased, unchanged or decreased after a course of injections of solution of acacia. An increase is most likely to occur when the initial colloid osmotic pressure is most subnormal.

5. These changes of colloid osmotic pressure, under the general regimen to which these patients were exposed, appear essentially unrelated to the degree of effectiveness of the treatment.

ADRENOCORTICAL COMPOUNDS IN THE BLOOD

RELATION OF THEIR QUANTITY TO ARTERIAL HYPERTENSION, RENAL INSUFFICIENCY AND CONGESTIVE HEART FAILURE

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The widespread but frequently contradicted belief that the adrenal glands play an active and substantial role in almost all forms of arterial hypertension is based on the following facts:

1. Tumors both of adrenal medullary and of adrenal cortical tissue have often been found to be accompanied by transitory or permanent arterial hypertension, either without clinical signs of severe renal damage, a condition simulating essential hypertension, or with albuminuria, isosthenuria, retention of nonprotein nitrogen, etc., a condition simulating malignant nephrosclerosis. In cases of the latter type autopsy has frequently revealed complete absence of morphologic changes in the kidneys. The pathogenetic significance of pheochromocytoma in cases of hypertension has been evidenced by spectacular curative results obtained by removal of the tumor (Pincoffs,¹ Brunschwig, Humphreys and Roome² and others). The literature concerning the relation of tumors of the adrenal glands to hypertension in general has recently been reviewed by Bauer³ and by Nuzum and Dalton.⁴

2. Both abnormally large adrenal glands (Opsahl,⁵ von Lucadou,⁶ Goldzieher⁷ and others) and cortical adenomas (Neuhaus⁸) are by far

This study was aided by a grant from the Rockefeller Foundation.

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1. Pincoffs, M. C.: Paroxysmal Hypertension Associated with Suprarenal Tumor, J. A. M. A. **93**:63 (July 6) 1929.

2. Brunschwig, A.; Humphreys, E., and Roome, N.: The Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, Surgery **4**:361-370, 1938.

3. Bauer, J.: Der Einfluss der Nebennieren und Hypophyse auf die Blutdruckregulation, Klin. Wchnschr. **11**:361-367, 1935.

4. Nuzum, F. R., and Dalton, J. W.: Paroxysmal and Persistent Hypertension in Association with Lesions of the Adrenal Glands, Am. Heart J. **16**: 643-662, 1938.

5. Opsahl, R.: Zur Pathogenese der arteriellen Hypertension, Acta med. Scandinav., 1938, supp. 92, pp. 1-262.

6. von Lucadou, W.: Die Nebennieren bei der Hypertonie, Klin. Wchnschr. **14**:1529-1530, 1935.

(Footnotes continued on next page)

more common in hypertensive persons than in normal persons, although they are by no means always absent in the latter. Besides, the adrenal cortex is usually hyperplastic in cases of Cushing's syndrome, which is almost always accompanied by arterial hypertension. The musculature of the adrenal veins, which is supposed to be of importance in secretory activities of the adrenal glands, has been found by Goldzieher and Sherman⁹ and by Allen¹⁰ to be hypertrophic in cases of hypertension.

3. Low blood pressure is a characteristic feature of adrenal insufficiency. It can be raised to normal, or even beyond normal, by the administration of cortical extracts and analogous synthetic products (Thaddea,¹¹ Ferrebee and collaborators,¹² McCullagh and Ryan¹³ and others). Injection of epinephrine hydrochloride produces more or less marked, but transitory, elevation of blood pressure. This is greatly enhanced by pretreatment with desoxycorticosterone acetate (Raab¹⁴). Prolonged administration of desoxycorticosterone acetate and other steroid derivatives has been found to cause long-lasting high elevations of blood pressure in rats (Grollman, Harrison and Williams¹⁵).

4. Experimental renal hypertension due to artificial ischemia of the kidneys is partly reduced by removal of the adrenal glands, but it can be restored by the administration of cortical extract (Goldblatt,¹⁶ Page,¹⁷ Collins and Wood¹⁸ and others). This phenomenon seems to be due

7. Goldzieher, M.: Ueber die Nebennieren bei Hochdruck und Arteriosklerose, *Virchows Arch. f. path. Anat.* **280**:749-755, 1931.

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9. Goldzieher, M. A., and Sherman, J.: Hypertrophy of Muscle in Suprarenal Vein in Hypertension, *Arch. Path.* **5**:1-12 (Jan.) 1928.

10. Allen, E. V.: The Suprarenal Glands and Hypertension, *Ann. Int. Med.* **3**:153-174, 1930.

11. Thaddea, S.: *Die Nebennierenrinde*, Leipzig, Georg Thieme, 1936.

12. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters, *J. A. M. A.* **113**:1725-1731 (Nov. 4) 1939.

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16. Goldblatt, H.: The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* **11**:69-103, 1937.

17. Page, I. H.: The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Am. J. Physiol.* **122**:352-358, 1938.

18. Collins, D. A., and Wood, E. H.: Experimental Renal Hypertension and Adrenalectomy, *Am. J. Physiol.* **123**:224-232, 1938.

to an activating effect of cortical substance on the renal pressor substance, renin (Friedman, Somkin and Oppenheimer¹⁹).

5. Increased amounts of corticotropic hormone of the anterior lobe of the pituitary body have been found by Jores²⁰ and Bergfeld²¹ in the blood of a number of hypertensive patients and of persons with Cushing's disease.

Removal of the hypophysis reduces the blood pressure in animals with experimental renal hypertension, supposedly through secondary adrenal cortical hypofunction (Page and Sweet²²). In some cases of Cushing's syndrome hypertension was abolished, together with other symptoms, through roentgen irradiation of both the hypophysis and the adrenal glands (Cushing,²³ Jamin,²⁴ Dattner²⁵ and others).

6. Considerable amounts of adrenocortical hormonal compounds have been found to be present in the tissue of arterial walls. The highest concentration was found in a patient with a tumor of the adrenal cortex (Raab²⁶). Epinephrine itself is formed in the arterial walls by adrenergic neurons (Cannon and Lissák²⁷).

7. The progress of arteriosclerotic vascular changes is greatly enhanced by adrenal activity (Goldzieher,⁷ Paul²⁸ and others) and by the administration of adrenal extracts (Anitschkoff,²⁹ Danisch,³⁰

19. Friedman, B.; Somkin, E., and Oppenheimer, E. T.: The Relation of Renin to the Adrenal Gland, *Am. J. Physiol.* **128**:481-487, 1940.

20. Jores, A.: Ueber Hormonuntersuchungen beim Morbus Cushing, *Klin. Wchnschr.* **38**:1348-1351, 1935.

21. Bergfeld, W.: Klinische und biologische Untersuchungen zum Problem Hypophyse und Hochdruck, *Deutsches Arch. f. klin. Med.* **182**:101-111, 1938.

22. Page, I. H., and Sweet, I. E.: The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Am. J. Physiol.* **120**:238-245, 1937.

23. Cushing, H.: "Dyspituitarism," Twenty Years Later, *Arch. Int. Med.* **51**:487-557 (April) 1933.

24. Jamin, F.: Die hypophysäre Plethora, Munich, J. F. Lehmann, 1935.

25. Dattner, B.: Zwei Fälle von Cushing'schem Adenom, *Wien. klin. Wchnschr.* **48**:809, 1935.

26. Raab, W.: Adrenocortical ("AC") Compounds in Human Organ Tissues, unpublished data.

27. Cannon, W. B., and Lissák, K.: Evidence for Adrenaline in Adrenergic Neurones, *Am. J. Physiol.* **125**:765-777, 1939.

28. Paul, F.: Die krankhafte Funktion der Nebenniere und ihr gestaltlicher Ausdruck, *Virchows Arch. f. path. Anat.* **282**:256-401, 1931.

29. Anitschkoff, N., in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.

30. Danisch, F.: Die sympathischen Ganglien in ihrer Bedeutung für die Cholesterinsklerose des Kaninchens, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:333-399, 1928.

Hueck,³¹ Raab³²). On the other hand, arteriolosclerosis of the cerebral vasomotor centers and of the kidneys produces the most outstanding mechanisms of hypertension (central and renal).

Despite the convincing character of many of the aforementioned observations, there has prevailed among a great number of investigators a deep-rooted doubt of any fundamental importance of the adrenal glands in the pathogenesis of arterial hypertension since the first claims of the presence of abnormal amounts of epinephrine in the serum of hypertensive persons (Schur and Wiesel³³) were thoroughly discredited by O'Connor.³⁴ An extensive and partly contradictory literature (Hantschmann³⁵) concerning vasopressor substances in various types of hypertension has as its climax the discovery and isolation of hypertenin (Westphal and Sievert³⁶) and angiotenin (Page and Helmer³⁷), but it gives no evidence of abnormally high epinephrine levels in the blood, except in a few instances of paroxysmal attacks of hypertension and of adrenal medullary tumors (Brandt and Katz,³⁸ Ernould and Picard³⁹). Only Kuré and collaborators⁴⁰ and Giordano and Zeglio⁴¹ claimed to have found the epinephrine content of the blood somewhat higher in persons with hypertensive and nephritic disease than in normal

31. Hueck, W.: Referat über den Cholesterinstoffwechsel, Verhandl. d. deutsch. path. Gesellsch., 1925, pp. 18-66.

32. Raab, W.: Arteriosklerose-Entstehung und Nebennieren-Lipoid-Adrenalin-("NLA")-Komplex, Ztschr. f. d. ges. exper. Med. **105**:657-678, 1939.

33. Schur, J., and Wiesel, J.: Ueber eine der Adrenalinwirkung analoge Wirkung des Blutserums von Nephritikern auf das Froschauge, Wien. klin. Wchnschr. **20**:699, 1907.

34. O'Connor, J. M.: Ueber den Adrenalingehalt des Blutes, Arch. f. exper. Path. u. Pharmacol. **67**:195, 1912.

35. Hantschmann, L.: Vasokonstriktorische Substanzen und Hochdruck, Ergebn. d. inn. Med. u. Kinderh. **49**:311-336, 1935; Ueber vasokonstriktorisches wirkende Stoffe im Blut mit besonderem Hinblick auf das Problem des Hochdruckes, Ztschr. f. d. ges. exper. Med. **96**:442-467, 1935.

36. Westphal, K., and Sievert, C. M.: Ueber den Reizstoff der genuinen Hypertonie, Ztschr. f. klin. Med. **133**:223-370, 1938.

37. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotenin) Resulting from the Reaction Between Renin and Renin-Activator, J. Exper. Med. **71**:29-42, 1940.

38. Brandt, F., and Katz, G.: Ueber den Nachweis von Adrenalinsekretion beim Menschen, Ztschr. f. klin. Med. **123**:40-50, 1933.

39. Ernould, H., and Picard, E.: Un cas de sympathome sympathogonique avec hypertension artérielle paroxystique, Rev. belge sc. méd. **6**:223-251, 1934.

40. Kuré, K.; Nakaya, T.; Murakami, S., and Okinaka, S.: Hyperadrenalinämie bei der essentiellen Hypertonie und ihre Behandlung durch Atropin, Klin. Wchnschr. **12**:454-458, 1933.

41. Giordano, C., and Zeglio, P.: Studi sull' adrenalina: L'adrenalinemia nell'ipertensione arteriosa, Arch. per le sc. med. **68**:1-30, 1939.

persons. Hantschmann,³⁵ Kahlson and von Werz,⁴² Hülse,⁴³ Westphal and Sievert,³⁶ Vogt⁴⁴ and others, however, explicitly denied the identity with epinephrine of those vasoconstrictor substances which are present in the serum of hypertensive persons.

Konschegg⁴⁵ found increased amounts of stable vasopressor epinephrine-lipoid compounds in the blood both of persons with essential and of persons with renal hypertension. From these compounds, which were obtained through hot alcoholic extraction of the dried blood and which differ from epinephrine, the latter substance could be slowly liberated through prolonged exposure to acids. Hereby the extracts decreased in vasoconstrictor efficiency. On the other hand, if the extracts were brought together with certain lipoids obtained from organs and from blood, epinephrine disappeared from the mixture and a compound with greater vasoconstrictor efficiency was formed.

According to Konschegg and Monauni,⁴⁶ quantitative determination of the amount of epinephrine obtainable from alcoholic extracts of blood with a modification of the method of Stuber, Russmann and Proebsting⁴⁷ revealed rather constant figures for normal persons. In cases of essential hypertension epinephrine was only irregularly and insignificantly increased. In cases of renal hypertension, however, it was almost always considerably augmented.

Bohn and co-workers⁴⁸ were unable to detect pressor substances in the blood of normal persons and in that of patients with essential hypertension, while they did find such substances in the blood of patients with renal hypertension. This was apparently due to their

42. Kahlson, G., and von Werz, R.: Ueber Nachweis und Vorkommen der gefäßverengernden Substanzen im menschlichen Blute, *Arch. f. exper. Path. u. Pharmacol.* **148**:173-197, 1929.

43. Hülse, W.: Untersuchungen über gefäßverengernde Stoffe im Blute, *Klin. Wchnschr.* **1**:2140, 1922.

44. Vogt, H.: Untersuchungen über vasopressorische Stoffe bei der essentiellen Hypertonie und beim Kaolinhochdruck des Hundes, *Klin. Wchnschr.* **33**:1148-1151, 1938.

45. Konschegg, T.: Adrenalin, Nebennieren und Blutdruck, *Ztschr. f. d. ges. exper. Med.* **81**:559-627, 1932; Experimenteller Beitrag zur Rolle des Blutes beim Blutdruck, *Wien. klin. Wchnschr.* **48**:1250-1252, 1935.

46. Konschegg, T., and Monauni, J.: Quantitative Bestimmung des Adrenalinalingehaltes der vasopressorischen Substanz, *Ztschr. f. klin. Med.* **131**:99-111, 1936.

47. Stuber, B.; Russmann, A., and Proebsting, E. A.: Ueber eine chemische Methode des Adrenalin-nachweises, *Ztschr. f. d. ges. exper. Med.* **32**:448-454, 1923.

48. Bohn, H.; Schlapp, W., and Stern, K.: Untersuchungen zum Mechanismus des blassen Hochdrucks, *Ztschr. f. klin. Med.* **127**:226-232, 1934. Bohn, H., and Schlapp, W.: Weitere Erfahrungen über den Nachweis pressorischer Stoffe im Blute beim blassen Hochdruck, *ibid.* **127**:233-242, 1934.

using cold alcoholic extraction, rather than Konschegg's method of hot alcoholic extraction, which yielded much larger amounts of lipid compounds.

In the conclusion of one of their papers Konschegg and Monauni⁴⁹ made the following statement:

We assume that the synthesis of epinephrine and lipoids which occurs in vitro also occurs in vivo. The resulting product will depend on the amount of epinephrine secreted by the adrenal glands and the amount, quality and state of solubility of the lipoids which are forming compounds with epinephrine . . . It is conceivable that in essential hypertension influences from the hypophysis will induce the adrenal glands to secrete a vasoconstrictor substance which is particularly effective because of changes in the lipoidal components, despite an insignificant increase of epinephrine.

Although Konschegg's work has been casually cited by many authors, no one has given serious consideration to the possibility that it furnishes the clue to contradictory results of previous investigators and to various problems of hormonal physiology and pathology. It becomes even more important in the light of recent recognition of the lipoidal nature of cortical hormones and of the mutual correlations between adrenal cortex and adrenal medulla.

Such a relation is evident from morphologic facts, such as the intimate vascular connections between cortex and medulla (Kutschera-Aichbergen⁴⁹), the existence of structural corticomedullary units, or epinephrones (von Bergmann⁵⁰), and the migration of cortical lipoidal substances toward the medulla, where they come into contact with epinephrine (Westphal and Sievert,⁵⁶ Bennett⁵¹).

Furthermore, a chemical relation between cortical substances and epinephrine has been stated by Kendall and collaborators,⁵² Abelous and Argaud⁵³ and others. The vasoconstrictor effect of epinephrine is intensified when the drug is given in combination with adrenal cortex extract (Sanders⁵⁴) and desoxycorticosterone acetate (Raab¹⁴). Extracts of the adrenal glands, containing lipoids which in themselves

49. Kutschera-Aichbergen, H.: *Ueber Herzschwäche*, Berlin, Urban & Schwarzenberg, 1929.

50. von Bergmann, G.: *Pathogenese und Therapie der Arteriosklerose*, Cong. internat. de l'Union therap. **1**:30-59, 1937.

51. Bennett, H. S.: *Localization of Adrenal Cortical Hormones in the Adrenal Cortex of the Cat*, Proc. Soc. Exper. Biol. & Med. **42**:786, 1939.

52. Kendall, E. C.; Mason, H. L.; McKenzie, B. F.; Myers, C. S., and Koelsche, G. A.: *Isolation in Crystalline Form of the Hormone Essential to Life from the Suprarenal Cortex*, Proc. Staff Meet., Mayo Clin. **9**:245, 1934.

53. Abelous, J. E., and Argaud, R.: *Compt. rend. Acad. d. sc.* **193**:369, 1931.

54. Sanders, E.: *Ueber die Wirkung von reinem Adrenalin und Nebennieren-extrakten per os und am isolierten Organ*, Arch. f. exper. Path. u. Pharmacol. **188**:657-668, 1938.

are inactive, exert a much stronger effect than could be accounted for by their content of epinephrine alone (Sanders⁵⁴). Stimuli which provoke discharges of epinephrine from the adrenal medulla cause at the same time hyperemia of the cortex (Sjöstrand⁵⁵).

In view of all these facts, a close functional synergism between the adrenal cortex and the adrenal medulla becomes probable. This seems to be true also with regard to the role of the adrenal glands in the origin of arterial hypertension.

METHOD

In an analysis of a method which was originally designed by Shaw⁵⁶ for the determination of epinephrine in the blood, it was found that this method yields figures which represent not pure epinephrine but chiefly compounds containing epinephrine and hormonal sterols, probably desoxycorticosterone in particular (Raab⁵⁷). Analogous compounds could be synthesized *in vitro*. They were disintegrated by acids. They could be quantitatively recovered in hot alcoholic extracts of blood, but not in cold alcoholic extracts. Thus, these adrenocortical compounds behaved essentially the same as the epinephrine-lipoid compounds described by Konschegg,⁴⁵ at a time when the chemical nature of the lipid-like cortical hormones was not yet known. No other substances were found participating in the colorimetric results of the modified method of Shaw,⁵⁶ except ascorbic acid, which may form from 10 to 50 per cent of the calculated total amount of color-giving material. The modifications of Shaw's method for the determination of adrenocortical compounds in blood and tissue have been published in *Endocrinology* (Raab⁵⁷).

In view of the fact that ascorbic acid forms, as a rule, only a minor fraction of the color-giving material in the blood and tissues, the term "adrenocortical compounds" will be used hereafter in referring to the total readings for the blood. All figures were obtained from determinations made in duplicate.

EFFECTS OF MUSCULAR EXERCISE ON THE LEVEL OF ADRENOCORTICAL COMPOUNDS IN THE BLOOD

Normal Persons.—In 51 normal persons, from 13 to 74 years of age, the level of adrenocortical compounds in venous blood during fasting was found to range between 60 and 222 color units per cubic centimeter, with an average of 156 color units per cubic centimeter (table 1). The color unit is based on comparison with a standard solution containing 100 millimicrograms of epinephrine hydrochloride per cubic centimeter and giving the colorimetric effect of 100 color units.

55. Sjöstrand, T.: On the Capillary Circulation of Blood in the Suprarenal Body of Mice, *Skandinav. Arch. f. Physiol.* **71**:85-122, 1934.

56. Shaw, F. H.: The Estimation of Adrenaline, *Biochem. J.* **32**:19-25, 1938.

57. Raab, W.: The Presence and Chemical Determination of Adreno-Cortical ("AC") Compounds in the Blood, *Endocrinology* **28**:325-336, 1941; Distribution of Adreno-Cortical ("AC") Hormones in the Tissues of the Rat Under Normal and Experimental Conditions, *ibid.* **29**:126-136, 1941.

Although it is not possible to differentiate exactly the individual quantities of the substances which are represented in the aforementioned figures, there exists a ratio (Shaw⁵⁶ and Raab⁵⁷), obtained by certain

TABLE 1.—*Data on the Level of Adrenocortical Compounds in Blood of Normal Persons*

Case No.	Sex	Age, Years	Smoker	Blood Pressure, Mm. of Mercury		Pulse Rate, Beats per Minute	Adrenocortical Compounds in the Blood, Color Units per Cc.
				Systolic	Diastolic		
1.....	♂	23	+	130	70	80	60
2.....	♂	24	+	120	80	76	60
3.....	♂	20	?	122	70	100	77
4.....	♂	24	—	122	96	86	84
5.....	♂	13	—	116	80	88	102
6.....	♂	44	—	130	80	82	113, 132, 156, 83, 126, 164
		45	160
		46	159
7.....	♂	28	+	118	50	72	114
8.....	♂	14	—	112	40	?	115
9.....	♂	21	?	120	85	?	121
10.....	♂	15	—	116	60	?	125
11.....	♂	49	—	106	76	86	127
12.....	♂	17	—	120	70	58	128
13.....	♂	23	—	126	76	92	131
14.....	♂	26	—	122	72	76	131
15.....	♂	63	+	110	60	?	135
16.....	♂	26	+	110	70	96	140, 162
17.....	♂	60	—	130	76	60	141
18.....	♂	25	—	146	90	84	148
19.....	♂	72	?	130	70	?	152
20.....	♂	26	?	120	80	?	158
21.....	♂	22	—	130	50	82	158
22.....	♂	23	++	120	70	65	158
23.....	♂	29	?	122	80	?	158
24.....	♂	60	+	150	84	?	158
25.....	♂	24	—	110	70	108	160
26.....	♂	23	?	115	70	?	160
27.....	♂	29	—	128	70	84	162
28.....	♂	23	++	134	70	104	162
29.....	♂	22	+	110	66	68	165
30.....	♂	37	—	140	98	96	167
31.....	♂	27	+	118	80	72	171
32.....	♂	23	?	120	80	?	177
33.....	♂	63	+	116	68	?	179
34.....	♂	26	+	102	56	88	180
35.....	♂	74	++	106	60	78	182
36.....	♂	27	—	128	70	66	189
37.....	♂	24	++	92	60	80	190
38.....	♂	34	?	104	70	64	191
39.....	♂	27	++	116	50	76	196
40.....	♂	31	++	130	70	?	200
41.....	♂	32	+	126	80	?	200
42.....	♂	20	++	112	0	72	201
43.....	♂	22	+	116	76	62	203, 186
44.....	♂	25	++	110	70	?	203
45.....	♂	27	—	110	70	84	203
46.....	♂	48	++	96	0	62	203
47.....	♂	40	+	150	80	?	206
48.....	♂	43	?	112	70	80	212
49.....	♂	19	?	122	70	?	214
50.....	♂	48	?	152	100	?	218
51.....	♂	42	+	120	80	?	222
Average.....		32	..	118	68	74	156

chemical procedures, which allows some conclusions as to the qualitative composition of the adrenocortical compounds in a given specimen of blood. For pure epinephrine the ratio is 1:3.5; for pure ascorbic acid, 1:0.3; for desoxycorticosterone, 1:1.2 and for synthetic epinephrine-

desoxycorticosterone compounds, 1:1.1. In normal blood the ratio for the adrenocortical compounds was found to range from 1:0.7 to 1:1.1, thus corresponding most closely to the ratio for synthetic adrenocortical compounds plus a varying amount of ascorbic acid.

When examined on different days, the blood of normal persons was found to have a fairly constant content of adrenocortical compounds (cases 6, 16 and 43; in the first case the readings were obtained within a period of two years).

Three quarters of the persons with a level of more than 150 color units per cubic centimeter were smokers, while only one quarter of the persons with a lower level smoked.

Fourteen normal persons were given muscular exercise tests (performing 30 genuflections or running up 42 to 68 steps, table 2). The level of adrenocortical compounds in the blood was determined before and two to five minutes and again fifteen minutes after exercise.

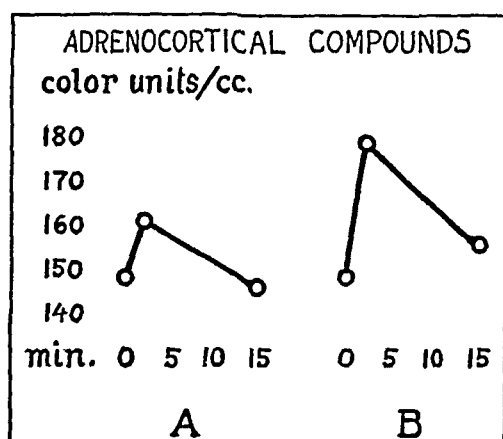


Fig. 1.—Average curves for the changes in the levels of adrenocortical compounds in the blood after exercise in (A) 14 normal subjects and (B) 25 patients with arterial hypertension.

In half of the cases there was a slight fall in the level; in others it rose slightly or moderately (11 to 37 color units per cubic centimeter), and in only 1 case was there a marked rise (82 color units per cubic centimeter) two minutes after exercise, with a subsequent return toward the original level. The average curve of change in the level of adrenocortical compounds in the blood induced by exercise is shown in figure 1.

Neither the original level of adrenocortical compounds nor the intensity of their reaction to exercise showed a parallelism with the height of blood pressure.

The behavior of the specific ratio revealed in several instances an increased epinephrine concentration in the secretion of adrenocortical compounds immediately following physical exercise.

TABLE 2.—Changes in Blood Pressure Pulse Rate and the Level of Adrenocortical Compounds in the Blood of Normal Persons Induced by Muscular Exercise

Case No.	Day	Sex	Age, Years	Blood Pressure (Systolic), Mm. of Mercury				Blood Pressure (Diastolic), Mm. of Mercury				Pulse Rate, Beats per Minute				Adrenocortical Compounds In the Blood, Color Units per Cc.			
				Exercise	Immediately After Exercise		15 Minutes After Exercise	Before Exercise	Exercise	Immediately After Exercise		15 Minutes After Exercise	Before Exercise	Exercise	2-5 Minutes After Exercise	15 Minutes After Exercise	Maximal Deviation from Resting Level		
					Exercise	15 Minutes After Exercise				Exercise	15 Minutes After Exercise								
4	9/28/39	♂	24	42 stairs	122	132	118	96	80	80	116	86	88	84	71	92	-13		
6	8/ 5/39	♂	44	30 genuflections...	113	116	130	+17		
	68 stairs			130	160	120	80	90	80	...	132	113	144	+12					
	68 stairs			126	103	138	+42*						
	30 genuflections			130	206	132	80	90	80	122	160	191	160	+31					
11	11/13/39	♂	49	42 stairs	106	92	86	76	63	66	116	86	82	127	209	149	+82		
13	4/29/40	♂	23	42 stairs	126	150	120	76	0	85	132	92	84	136	159	141	+23		
14	5/ 3/40	♂	26	42 stairs	122	160	122	72	0	76	128	76	80	131	165	118	+34		
17	3/11/40	♂	60	42 stairs	130	180	122	76	70	70	108	60	62	141	135	125	-16		
22	10/24/39	♂	23	42 stairs	120	150	120	70	20	72	108	68	76	133	179	129	-29		
25	8/16/39	♂	24	42 stairs	160	162	139	-21		
26	6/16/39	♂	23	68 stairs	160	170	180	+20		
28	11/ 6/39	♂	23	42 stairs	134	172	152	70	0	60	132	104	100	162	173	167	+11		
34	5/ 7/40	♂	26	42 stairs	102	130	100	56	0	60	120	88	86	180	173	139	-21		
37	5/13/40	♂	24	42 stairs	92	98	92	60	50	62	150	80	90	190	227	186	+37		
39	10/24/39	♂	27	42 stairs	110	120	126	50	0	80	120	76	66	196	183	169	-27		
40	8/19/39	♂	31	42 stairs	130	155	130	70	60	72	200	186	190	-14		
Average.....					120	146	118	72	75	71	123	82	81	150	165	148	+10		

* A few hours before the onset of an attack of grip, with fever.

Patients with Essential Hypertension.—This group of subjects (table 3) comprised 36 patients with a systolic blood pressure of 150 to 330 mm. of mercury (average 193 mm.) and with no clinical signs of renal involvement, except slight traces of albumin in the urine in 9 cases. The hyperventilation test for hyperirritability of the vasomotor centers (Raab⁵⁸) was carried out on 13 patients, with a posi-

TABLE 3.—Data on Patients with Essential Hypertension

Case No.	Sex	Age	Blood Pressure, Mm. of Mercury		Pulse Rate, Beats per Min.	Albumin in Urine	Electrocardiogram	Comment	Adrenocortical Compounds in the Blood, Color Units per Cc.
			Systolic	Diastolic					
52	♂	74	330	0	?	±	?	HV,* 84 mm.; diabetes.....	81
53	♂	62	260	140	?	?	?	Cerebral arteriosclerosis.....	214
54	♂	64	250	110	100	—	?	HV, 44 mm.;	159
55	♀	48	250	140	88	—	±	HV, 20 mm.; headaches.....	213
56	♀	43	230	130	?	±	?	Artificial menopause.....	83
57	♀	38	228	122	86	—	?	HV, 52 mm.; headaches.....	146
58	♀	23	222	110	84	—	—	No subjective complaints.....	77
59	♀	58	220	84	82	—	+	HV, 48 mm.; angina pectoris.....	83
60	♀	66	220	130	88	±	+	HV, 56 mm.;	137
61	♀	49	216	98	96	±	+	Angina pectoris.....	257
62	♀	50	212	130	88	±	±	HV, 40 mm.; headaches.....	203
63	♀	55	204	130	103	±	+	HV, negative; no complaints.....	178
64	♀	20	204	140	76	—	+	HV, negative; headaches.....	126
65	♀	41	200	130	92	—	?	HV, 40 mm.; headaches.....	60
66	♀	45	200	130	96	—	±	HV, 34 mm.; headaches.....	193
67	♀	54	200	106	100	—	±	HV, negative, angina pectoris.....	176
68	♀	64	190	100	?	—	?	Cerebral arteriosclerosis.....	186
69	♀	65	188	80	94	—	—	HV, 38 mm.; angina pectoris; diabetes.....	131
70	♀	64	180	120	70	—	+	Cerebral arteriosclerosis.....	60
71	♀	25	178	80	?	—	?	No subjective complaints.....	179
72	♀	47	174	100	68	—	?	Artificial menopause; neurosis.....	189
73	♀	53	172	86	?	—	?	Hyperthyroidism; B. M. R. +28%... ..	126
74	♀	67	170	120	92	—	±	Angina pectoris.....	152
75	♀	73	170	80	84	—	+	Angina pectoris.....	138
76	♀	56	170	80	?	—	?	No subjective complaints.....	114
77	♀	72	165	85	?	±	?	Diabetic gangrene.....	180
78	♀	52	160	60	?	—	?	No subjective complaints.....	200
79	♀	44	160	70	176	—	?	Hyperthyroidism; B. M. R. +63%... ..	135
80	♀	63	160	80	80	?	—	Angina pectoris.....	200
81	♀	48	152	100	?	—	?	No subjective complaints.....	218
82	♀	78	150	80	?	±	—	Diabetes.....	86
83	♀	69	150	90	136	±	?	Bronchitis.....	203
84	♀	40	150	80	?	—	?	No subjective complaints.....	206
85	♀	60	150	84	?	—	?	No subjective complaints.....	158
86	♀	59	150	70	80	—	±	Angina pectoris.....	131
87	♀	59	150	0	128	—	?	Hyperthyroidism; B. M. R. +26%; diabetes.....	114
Average....		54	193	97	95	154

* HV = hyperventilation test. The fall of blood pressure is measured in millimeters of mercury.

tive result (drop of blood pressure) for 10 of them, suggesting cerebral arteriosclerotic ischemia of the vasomotor center areas.

58. Raab, W.: Die Beziehungen zwischen CO₂-Spannung und Blutdruck bei Normalen und Hypertonikern, Ztschr. f. d. ges. exper. Med. 68:337-370, 1929; The Hormonal, Central and Renal Origin of "Essential" Hypertension (Cerebral and Renal Arteriosclerotic Ischemia as Causal Factors), Ann. Int. Med. 14: 1981-2007, 1941.

The levels of adrenocortical compounds in the blood of persons in this group, both during fasting and at rest, ranged from 60 to 257 color units per cubic centimeter, with an average of 154 color units—values practically identical with those recorded for normal persons. Some of these hypertensive patients who were suffering from diabetes mellitus, angina pectoris or hyperthyroidism did not reveal any peculiarities of the level of adrenocortical compounds as determined during physical rest. The specific ratios varied from 1:0.7 to 1:1.2, in analogy to those found for normal persons. There was no noticeable relation between the blood pressure and the level of adrenocortical compounds in the blood.

The reaction of these patients to physical exercise (table 4) differed from that of normal persons in that diminutions of the level of the adrenocortical compounds took place in only 7 out of 25 patients, while in 18 patients there were elevations, most of them of a degree considerably higher than those in the normal persons. The peak of the curve for adrenocortical compounds was usually reached two or three minutes after exercise, with a subsequent return toward normal, and in only 4 cases was there a belated rise, with the maximum occurring after fifteen minutes. Figure 1 *B* shows the average curve for all patients with essential hypertension.

The changes in blood pressure and in pulse rate after exercise were approximately of the same order as those occurring in the normal persons. There was no parallelism between the intensity of the reaction of the blood pressure to exercise and the amount of adrenocortical compounds in the blood.

Patients with Renal Hypertension but Without Renal Insufficiency.—This group of patients (table 5) included 9 who showed arterial hypertension with signs of definite renal involvement but whose condition did not reveal the criteria of severe impairment of renal function. Three (cases 88, 92 and 93) had arteriosclerosis. In their blood the levels of adrenocortical compounds were at or above the upper limit of normal. Four patients (cases 89, 90, 91 and 95) were women in whom complications of pregnancy seemed the outstanding renal etiologic factor. The oldest of them (case 89), with a history of many pregnancies, who had intense albuminuria and hemorrhages of the retina and the second oldest (case 95) had abnormally high levels of adrenocortical compounds; the values for the 2 younger patients, whose conditions were less severe, were within normal range. One patient (case 94) had acute nephritis subsequent to tonsillitis with abscess formation. The level of adrenocortical compounds in his blood was slightly above the normal maximum shortly after the onset of nephritis but returned to normal with clinical improvement.

TABLE 4.—Changes in Blood Pressure, Pulse Rate and the Level of Adrenocortical Compounds in the Blood of Patients with Essential Hypertension Induced by Muscular Exercise *

Case No.	Sex	Age, Years	Blood Pressure (Systolic), Mm. of Mercury			Blood Pressure (Diastolic), Mm. of Mercury			Pulse Rate, Beats per Minute		Adrenocortical Compounds in the Blood, Color Units per Cc.			
			Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	Immediately After Exercise	15 Minutes After Exercise	Before Exercise	Immediately After Exercise	2 to 5 Minutes After Exercise	15 Minutes After Exercise	Maximal Deviation from Resting Level	
72	♀	47	174	180	166	100	88	102	68	108	106	162	-27	
88	♀	52	238	250	218	140	120	140	106	160	263	248	-30	
76	♂	56	170	186	150	80	0	50	110	90	-24	
62	♀	50	212	222	214	130	120	120	88	118	210	190	-18	
114	♂	81	250	270	252	56	72	60	56	72	50	60	-20	
90	♀	29	166	190	160	110	116	108	84	112	139	135	-11	
63	♂	55	204	240	200	130	170	134	108	148	190	156	-22	
60	♀	65	220	230	210	130	130	126	88	116	168	143	+20	
54	♀	64	250	264	240	110	90	116	100	112	181	173	+22	
58	♀	23	222	250	228	110	110	110	84	120	70	100	+23	
75	♀	73	170	182	172	80	100	92	84	96	171	140	+33	
69	♀	65	188	220	168	80	60	80	94	136	162	152	+31	
67	♀	54	200	220	206	100	120	106	100	140	160	206	+30	
59	♂	58	212	220	222	84	86	96	82	120	135	98	+52	
93	♂	37	210	216	...	140	138	...	104	100	263	...	+48	
107	♂	67	170	190	130	110	100	70	202	145	+62	
86	♂	59	150	180	148	70	110	70	80	120	180	116	+57	
61	♀	49	216	280	212	98	0	100	96	148	310	233	+53	
74	♂	67	170	184	180	120	120	120	215	150	+63	
70	♂	64	180	190	150	120	124	120	76	88	131	81	+71	
66	♀	45	200	225	190	130	120	132	96	136	197	257	+64	
65	♂	41	200	244	194	130	126	130	92	160	157	100	+97	
71	♂	25	178	251	241	+72	
56	♀	43	230	250	226	130	120	136	119	220	+137	
80	♂	63	160	186	162	80	90	84	80	76	305	190	+105	
Average.....		53	197	218	190	106	101	104	88	120	181	158	+36	

* The exercise consisted of climbing 43 steps, except in case 75, in which it consisted of sitting up in bed ten times.

TABLE 5.—Data on Patients with Renal Hypertension Without Renal Insufficiency

Case No.	Day	Sex	Age	Blood Pressure, Mm. of Mercury		Pulse Rate, Beats per Min.	Albu- min in Urine, Per- centage	Specific Gravity of Urine	Non- protein Nitro- gen, Mgs. per 100 Cc.	Hyper- tension Test	Electro- cardio- gram Changes	Ocular Changes	Red Blood Cells	Hemo- globin Concen- tration per Cc.	Adrenocortical Compounds in the Blood, Color Units	Comment
				Sys- tolic	Diastolic											
88	10/23/30	♀	52	200	160	100	20	1.008-1.022	34	Neg.	++	?	4,100,000	85%	278	Headaches
89	5/21/40	♀	45	210	120	100	4-27	1.007-1.030	43	?	—	+	85%	245	Fifteen pregnancies; headaches
90	2/23/40	♀	29	166	110	84	4	1.010-1.012 (?)	?	?	—	—	4,200,000	71%	140	Three pregnancies; headaches
91	3/ 6/40	♀	22	170	120	72	5	?	?	?	?	—	91%	169	Pregnant 7 months
92	5/ 5/40	♀	25	190	120	?	2-30	?	?	?	?	+	3,300,000	55%	283	Convulsions several days before study; photophobia
93	4/ 7/40	♂	37	210	140	104	+	1.017-1.018	40	?	++	+	65%	220	
94	2/21/40	♂	32	188	114	?	+	1.015-1.030	43	?	—	—	3,400,000	68%	240	Acute nephritis after tonsillitis
95	3/ 9/40	150	110	...	+	135	Clinically improved
	7/15/40	♀	44	213	132	104	±	1.010-1.015	37	?	?	++	?	?	290	Headaches; four pregnancies
96	2/27/40	♂	2	160	90	98	1-21	1.010-1.030	43	+	—	—	4,200,000	122	Convulsions three weeks before study
	3/ 3/40	212	120	120	239	
	3/ 5/40	240*	138*	270*	After massage of right adrenal region
	3/ 6/40	196	110	200	
	3/ 8/40	256	132	302	
	3/16/40	204*	130*	112*	169*	One day after a series of roentgen irradiations of right adrenal
	3/27/40	224*	130*	165*	Twelve days after roentgen irradiation of right adrenal
	4/ 8/40	210	130	110	304	
	4/15/40	216*	120*	140*	190*	Three days after a series of roentgen irradiations of left adrenal
	4/24/40	180*	120*	100*	131*	In ether narcosis
	4/24/40	190*	130*	106*	207*	In narcosis 30 minutes after exposure of both adrenals and kidneys
Average.....			32	200	121	100	39	226	

* These figures were not included in the average calculation because of outward interference, such as massage or roentgen irradiation of the adrenal region.

Most interesting was case 96, which is reported in some detail.

Arterial hypertension was discovered in this 2 year old boy when he was examined because of convulsions, pallor and puffiness of the face. For several weeks his systolic blood pressure varied from 135 to 200 mm. of mercury but became gradually stabilized around 180 to 220 mm. The heart was considerably enlarged to the left. There was marked albuminuria, the amount of albumin reaching 21 per cent by volume. The nonprotein nitrogen content of the blood varied between 33 and 43 mg. per hundred cubic centimeters. The concentrating power of the kidneys, the eyegrounds and the blood count were practically normal. Also, the level of adrenocortical compounds in the blood was normal on the first determination, when the systolic blood pressure was comparatively low (160 mm. of mercury), but later it varied within higher levels as did the blood pressure. The highest value for these compounds (362 color units per cubic centimeter) was reached one day when the systolic blood pressure rose to its maximum of 256 mm. Massage in the region of the right adrenal gland seemed to cause a simultaneous rise of the blood pressure and the level of adrenocortical compounds. Roentgen irradiation of the right and later of the left adrenal gland was followed in each instance by a temporary drop of the content of adrenocortical compounds to normal, but there was no change in blood pressure. An exploratory transabdominal operation was performed on April 24, 1940, in order to permit inspection of the adrenal glands and the kidneys. No gross anomaly was noted. The level of adrenocortical compounds was found elevated half an hour after manipulation of the adrenal glands.

The pathogenetic mechanism in this rare case of infantile hypertension was interpreted as primary hyperfunction of the adrenal glands, without tumor formation, and subsequent precocious arteriolosclerotic involvement of the kidneys and the cerebral vasomotor centers. The importance of the latter factor was predicated on a positive reaction to the hyperventilation test (a drop of 46 mm. of mercury in the blood pressure during ten minutes of moderate passive hyperventilation).

The average level of adrenocortical compounds in the blood for the entire group of patients with hypertension and mild renal involvement was slightly above the normal maximum (table 8). The specific ratios were within the normal range.

Also, in the case of an 8 year old girl with a history of glomerulonephritis and symptoms of nephrosis (33 to 60 Gm. of albumin per hundred cubic centimeters, low values for plasma proteins, marked edema and 540 mg. of cholesterol per hundred cubic centimeters of blood), the level of adrenocortical compounds in the blood was above the normal maximum (231 color units per cubic centimeter), with a specific ratio of 1:1.11. The blood pressure was 105 mm. systolic and 68 mm. diastolic.

Patients with Renal Hypertension and Associated Renal Insufficiency.—Among 10 patients (table 6) with definite signs of renal functional insufficiency (isosthenuria, azotemia, changes of the eyegrounds

TABLE 6.—Data on Patients with Renal Hypertension Associated with Renal Insufficiency

Case No.	Day	Sex	Age	Blood Pressure, Mm. of Mercury		Pulse Rate, Beats per Min.	Albumin in Urine, Percentage	Specific Gravity of Urine	Non-protein Nitrogen, Mg. per 100 Cc.	Hyper-ventilation Test	Electrocardio-gram Changes	Red Blood Cells	Adrenocortical Compounds in the Blood, Hemo-globin Concentration per Cc.		Comment
				Sys-tolic	Diastolic								Hemo-globin Concentration per Cc.	Blood, Color, Units	
97	4/5/40	♂	53	230	140	62	+	1.008-1.012	80	Neg.	+	4,500,000	169	Eight days after attack of pulmonary edema
	5/23/40	222	140	68	3	—	—	200	Feels subjectively well
	11/22/40	..	54	220	110	72	10	1.009-1.011	190	—	..	4,000,000	227	Headaches
98	12/5/39	♂	39	200	130	98	++	1.013-1.016	104	+	+	4,000,000	78%	304	
99	9/8/39	♂	25	190	140	108	++	1.008-1.011	55	Neg	++	3,400,000	558	2½ months after resection of right splanchnic nerve
	9/11/39	220*	140*	116*	±	130	257*	After a series of roentgen irradiations of the adrenal glands
	9/16/39	230*	170*	130*	±	290*	7 days before death (6 days after irradiation of adrenal glands)
100	4/5/40	♂	52	235	140	100	++	1.008-1.010	171	Neg.	+	52%	362	
	4/8/40	242	130	96	377	
	4/15/40	230*	120*	90*	257	3 days after a series of roentgen irradiations of the adrenal glands
	4/22/40	170	85	?	556	A few hours before death (pulmonary edema)
101	4/25/40	♂	51	190	98	88	18	1.009-1.011	270	?	+	55%	302	
	4/30/40	192	100	92	333	543	4 days before death
102	5/8/40	♂	58	160	90	76	±	1.008-1.010	260	?	—	3,400,000	60%	562	4 days before death
103	12/3/40	♂	21	165	90	?	3-13	1.004-1.010	200	?	+	3,600,000	283	Plumbism (?); previous scarlet fever
104	12/3/40	♀	16	135	85	?	7/19	1.009-1.012	333	?	±	1,900,000	420	3 weeks before death
105	3/5/41	♀	8	162	90	?	15-30	1.005-1.015	100	?	++	3,100,000	362	1 day before death
118	9/10/41	♀	38	160	100	92	2	1.010	680	?	+	3,780,000	362	3 days before death
Average.....			38	205	126	87	208	372	

* These figures were not included in the average calculation because of outward interference.

and anemia) 1 (case 97) had a normal level of adrenocortical compounds in the blood at first. At that time he felt subjectively well and his condition was good except for an attack of pulmonary edema with subsequent temporary cardiac decompensation of a slight degree. Later, when his subjective condition had grown worse and the non-protein nitrogen of the blood had increased from 80 to 190 mg. per hundred cubic centimeters, the adrenocortical compounds in the blood were also found to have reached a pathologically high level. The conditions of the other 19 patients (cases 98 to 105 and case 118) were typical of an advanced stage of uremia. Seven of these patients died soon after examination. In 2 (cases 100 and 101) small granular kidneys were found. In 1 (case 102), whose blood pressure had always been relatively low, there was polycystic degeneration of both kidneys, with marked arteriolosclerosis of the parenchyma. In case 118 there was pyonephrosis. All of the patients with uremia had abnormally, and in part even excessively, high levels of adrenocortical compounds in the blood, reaching from 283 to as high as 562 color units per cubic centimeter.

In 2 patients (cases 99 and 100) roentgen irradiation of the adrenal glands (a total of 600 r over each gland, given in six doses) was followed by a marked fall of the level of adrenocortical compounds (54 and 32 per cent, respectively), but there was no distinct change in blood pressure.

One patient (case 99), a 25 year old man with malignant hypertension, had undergone an operation at the Massachusetts General Hospital three months prior to the first determination of adrenocortical compounds. An extensive resection of the right splanchnic nerve had been followed by some subjective improvement, fall of the systolic blood pressure from about 260 to about 200 mm. of mercury and diminution of the pulse rate from about 150 to about 110 beats per minute. Nevertheless, the content of adrenocortical compounds was extremely high (558 color units per cubic centimeter). Exercise induced a paradoxical fall of the level of these substances. The patient died two weeks later. No autopsy was done.

The average level of adrenocortical compounds in the blood of patients with renal hypertension and renal insufficiency was two and a half times as high as normal (table 8). The specific ratios were within normal range.

Patients with Congestive Heart Failure.—The group of 16 patients with congestive heart failure (table 7) overlaps in part the foregoing group of patients with renal hypertension and associated renal insufficiency with respect to those data in cases 97, 99, 100 and 101 which were obtained while the subjects were in a state of cardiac decompensation.

TABLE 7.—Data on Patients with Congestive Heart Failure

Case No.	Day	Sex	Age	Blood Pressure, Mm. of Mercury		Pulse Rate, Beats per Min.	Electrocardiogram	Dyspnea	Con- gestion of Liver	Edema	Cyanosis	Severity of Decom- pensation	Comment	Adrenocortical Compounds in the Blood, Color Units per Cc.
				Sys- tolic	Diastolic									
106	5/ 8/40	♂	64	150	110	130	++	++	+	+++	+	+++	Nonprotein nitrogen, 49 mg. per 100 cc...	240
107	8/17/39	♂	58	70	40	118	+	+++	+	+	+++	+++	Pulmonary edema; unconscious...	276
	8/19/39	165	70	116	+	+++	+	+	+++	+++	1 day before death.....	231
108	9/ 7/39	♂	70	140	90	72	+	++	+	+	++	+++	Temperature, 100-102 F.	236
	9/11/39	160	60	63	+	+++	+	+	++	+++	Temperature normal; mentally disturbed	166
109	4/ 5/40	♂	54	154	66	108	++	+++	+	+	+	+++	Alcoholic	146
110	8/11/39	♂	67	170	110	98	+	++	+	+	+	++	Angina pectoris	140
	10/29/39	100	60	90	+	++	++	++	++	++	Condition much worse than on August 11	232
101	4/25/40	♂	51	190	98	88	+	+	+	++	++	+++	Renal insufficiency; nonprotein nitrogen, 270 mg. per 100 cc.....	302
	4/30/40	192	100	92	+	+	+	+++	++	+++	3 days before death; nonprotein nitro- gen, 333 mg. per 100 cc.....	543
99	9/10/39	♂	25	230	170	130	++	++	±	+	++	+++	7 days before death; nonprotein nitro- gen, 133 mg. per 100 cc.....	290
100	4/ 5/40	♂	52	235	140	100	+	++	—	+	—	++	Renal insufficiency; nonprotein nitrogen, 171 mg. per 100 cc.....	362
	4/15/40	242	130	96	+	++	—	+	—	++	377
	4/22/40	170	85	?	+	+++	+	+	±	+++	A few hours before death; pulmonary edema	556
111	1/10/40	♀	63	170	80	104	+	+	+	+	+	++	Auricular fibrillation	181
112	9/29/39	♂	58	142	80	70	+	+	++	+	+	++	Angina pectoris	145
113	3/19/40	♀	59	100	98	90	++	++	+	++	+	++	Diabetes mellitus	100
114	3/25/40	♂	73	170	90	80	?	+	+	+	—	++	Angina pectoris	112
115	4/ 4/40	♂	88	156	110	56	++	+	++	+	—	++	11 days after coronary occlusion.....	102
97	4/ 5/40	♂	53	230	140	62	+	+	+	+	—	+	Renal insufficiency; nonprotein nitrogen, 80 mg. per 100 cc.....	169
116	8/ 8/39	♀	73	130	70	?	?	+	—	+	—	+	Diabetes mellitus	205
117	5/20/41	♀	56	178	100	?	+	++	+	++	+	++	Obesity	159
Average.....			61	169	93	93	229

The levels of adrenocortical compounds for the 16 patients with congestive heart failure ranged from 100 to 556 color units per cubic centimeter, with an average of 229 color units, which is slightly above the normal maximum. Although several patients had a normal level, a distinct tendency toward abnormally high levels was shown by most of the patients with a severe degree of congestive heart failure.

Two patients (cases 100 and 107) displayed a marked rise in the level of adrenocortical compounds during attacks of pulmonary edema.

TABLE 8.—*Average Results for All Groups*

Condition	Number of Sub-jects	Age, Yr.	Blood Pressure, Mm. of Mercury		Adrenocortical Compounds in the Blood, Color Units per Cc.			Specific Ratio, Average
			Sys-tolic	Dias-tolic	Mini-mum	Maxi-mum	Aver-age	
Normal.....	51	32	118	68	60	222	156	1:1.01*
Essential hypertension.....	36	54	193	97	60	257	154	1:1.16*
Renal hypertension without renal insufficiency.....	9	32	200	121	122	362	226	1:1.09*
Renal hypertension with renal insufficiency.....	9	38	203	128	169	562	373	1:0.99*
Congestive heart failure.....	16	61	169	96	100	556	229	1:1.01*

* The number of determinations of the specific ratio in each of the five groups of persons was as follows: 7, 6, 6, 7 and 7.

COMMENT

The results which are reported in the foregoing sections require a few words of comment concerning the grouping of the patients examined. The clinical subdivision of patients with arterial hypertension without signs of renal insufficiency, such as azotemia and isosthenuria, into one group with "essential" hypertension and another with "renal" hypertension is by necessity somewhat arbitrary, as the absence of clinical signs of major renal involvement does not exclude the possible presence of a moderate degree of renal arteriosclerosis, sufficient to participate as a pathogenic factor in the mechanism of essential, seemingly nonrenal, hypertension. On the other hand, hyperirritability and hyperirritation of the vasomotor centers due to arteriosclerotic cerebral anoxia, although most common in essential hypertension, are not infrequently present also in chronic renal hypertension. In fact, both pathogenic factors, renal and cerebral arteriolar sclerosis, are usually present at the same time, with one or the other prevailing. The hyperventilation test (Raab⁵⁸), which forms a convenient and rather reliable criterion for testing hyperirritability of the vasomotor centers in cases of arterial hypertension, gave positive results in 10 out of 13 cases of essential hypertension and negative results in 4 out of 6 cases

of renal hypertension. This behavior is in accordance with previous findings of Raab,⁵⁹ Dicker,⁶⁰ Voit and Cyba⁶¹ and others.

Human blood contains a certain amount of adrenocortical compounds, which consist of epinephrine and cortical sterols and which seem to form the bulk of physiologic adrenal secretion. The levels of adrenocortical compounds in the blood of 51 normal persons and those of 36 patients with essential hypertension did not show any significant difference, either in the range of variations or in the averages, which were practically identical in the two groups. Also, the qualitative composition (specific ratio) of the determined adrenocortical compounds and their content in epinephrine proper seemed to be about the same in the two groups. Nevertheless, the possibility of qualitative differences in molecular structure of the sterols cannot be excluded.

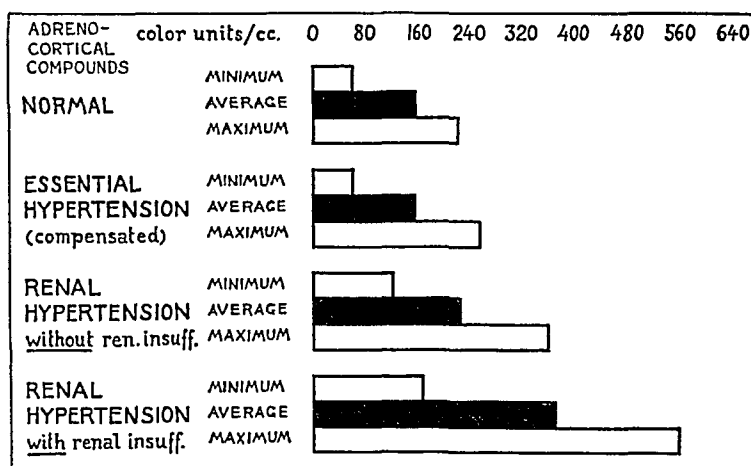


Fig. 2.—Summary of determinations of adrenocortical compounds in the blood of 51 normal persons and a total of 55 patients with various forms of arterial hypertension.

In patients with renal hypertension without signs of severe excretory renal insufficiency there was, with few exceptions, an obvious tendency toward levels of adrenocortical compounds which were higher than the normal maximum. In patients with severe renal insufficiency and uremia there were always abnormally, and in part excessively, high levels of adrenocortical compounds in the blood.

No distinct parallelism between levels of adrenocortical compounds and levels of blood pressure was observed in any of the groups men-

59. Raab, W.: Die zentrogenen Formen des arteriellen Hochdruckes, *Ergebn. d. inn. Med. u. Kinderh.* **46**:452-555, 1934.

60. Dicker, E.: Recherches cliniques sur la pathogénie de l'hypertension artérielle, *Acta med. Scandinav.* **92**:461-496, 1937.

61. Voit, K., and Cyba, J.: Das Verhalten des Blutdruckes bei Hyperventilation und Sauerstoffatmung, *München. med. Wchnschr.* **38**:1466-1468, 1933.

tioned, except in the case of a 2 year old child (case 96) with severe hypertension and renal involvement, in whom the adrenocortical compounds and the systolic blood pressure were found to reach their lowest and their highest levels simultaneously.

These findings are in accordance with those of Konschegg⁴⁵ and Konschegg and Monauni⁴⁶ with respect to the values for "lipoid-epinephrine compounds," which these authors have isolated from the blood both of normal persons and of persons with hypertension. These compounds seem to be closely related to, or even identical with, the adrenocortical compounds. Konschegg and Monauni found the content of epinephrine only irregularly and insignificantly increased in cases of essential hypertension, while it was "almost without exception markedly increased" in cases of renal hypertension. Nevertheless, the authors claimed that because of some peculiarities of the qualitative composition of the "lipoid-epinephrine compounds," their vasoconstrictor and pressor power is greater than normal in all types of hypertension (essential and renal) and that this action bears a certain ratio to the actual height of the blood pressure. My purely chemical data do not directly support this view, but neither can they invalidate it, as slight and colorimetrically undetectable alterations of the molecular structure of the adrenocortical compounds may suffice to influence their hormonal mode of action. According to Grollman, Harrison and Williams,¹⁵ desoxycorticosterone acetate has pressor qualities which are absent in the "natural cortical hormone." Kutschera-Aichbergen⁴⁹ described characteristic histochemical and quantitative changes in the lipid content of the adrenal cortex in cases of arterial hypertension and suggested an increased mobilization of such lipoids in persons with hypertensive disease. Koehler⁶² found that the amount of epinephrine in extirpated adrenal tissue of hypertensive patients was normal, or even slightly diminished.

Roentgen irradiation of the adrenal glands is likely to depress abnormally high levels of adrenocortical compounds, at least temporarily, without any distinct effect on the blood pressure. In another series of experiments concerning patients with angina pectoris, which will be published separately, it was found that normal resting levels of adrenocortical compounds are not depressed through roentgen irradiation of the adrenal glands with a moderate dose.

Discharges of adrenocortical compounds into the blood stream after muscular exercise were found to be irregular and of moderate intensity in normal persons, with 1 exception (case 11). In the majority of the patients with essential hypertension, on the other

62. Koehler, A. E.: The Epinephrin Content of Suprarenal Glands Surgically Removed in the Treatment of Essential Hypertension, *J. Biol. Chem.* **114**:lix, 1936.

hand, they were considerably more marked than in most of the normal persons, although they started from normal initial levels.

A slight or moderate fall of the adrenocortical compounds in the blood, as observed after exercise in several normal persons and in several hypertensive persons, does not exclude the possibility of an absolute increase of the epinephrine portion of the adrenocortical compounds after exercise. In fact, such a temporary change in the composition of the adrenocortical compounds was suggested by a series of determinations of the specific ratio.

The fundamental importance of discharges of epinephrine into the blood for the pathogenesis of anginal attacks in patients with coronary sclerosis (Raab ⁶³) was evidenced by the regular presence of intense discharges of adrenocortical compounds after exercise in patients with angina pectoris and by the disappearance of this characteristic phenomenon after therapeutically successful roentgen irradiation of the adrenal glands. The results of these investigations will be published separately.

Among patients with congestive heart failure, an increased level of adrenocortical compounds in the blood was found in the majority of those with the more severe involvement and during attacks of pulmonary edema. This seems to conform with a number of recent clinical and experimental observations concerning the toxic effects of adrenal cortical sterols (desoxycorticosterone, corticosterone) on cardiac muscle and on mineral water metabolism. Typical heart failure with edema (Pentschew, ⁶⁴ Kuhlmann and co-workers, ⁶⁵ Ferreeb and co-workers ¹²), pulmonary edema (Heni ⁶⁶) and changes in the electrocardiogram indicative of anoxia (Kuhlmann and co-workers ⁶⁵ Raab ¹⁴) are produced through overdosage with those sterols. Pulmonary edema, and even death, has been brought about in animals by the intravenous injection of alcoholic extracts of the adrenal glands containing cortical lipoids and epinephrine bound to them (Raab ⁸²). Injected epinephrine hydrochloride and desoxycorticosterone acetate was found to be absorbed and stored in relatively large amounts by the cardiac muscle of rats, with fatal result when a certain critical concentration in the myocardium was reached (Raab ⁶⁷).

63. Raab, W.: Roentgen Treatment of the Adrenal Glands in Angina Pectoris (One Hundred Cases), *Ann. Int. Med.* **14**:688-710, 1940.

64. Pentschew, A.: Folgen der Ueberdosierung des Nebennierenrindenhormons, *Klin. Wchnschr.* **50**:1570-1572, 1939.

65. Kuhlmann, D.; Ragan, C.; Ferreeb, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone Esters in Dogs, *Science* **90**:496-497, 1939.

66. Heni, F.: Klinisches zur Frage des Morbus Addison, *Klin. Wchnschr.* **18**:1052-1056, 1939.

67. Raab, W.: Adreno-Cortical ("AC") Hormones in the Heart Muscle of the Rat (Chemical Determinations), *Endocrinology*, to be published.

The well known anoxic effect of epinephrine on cardiac muscle has been carefully studied by Gremels⁶⁸ and Gollwitzer-Meier,⁶⁹ who stated that it is due not only to the increase of hemodynamic activity but to a specific metabolic process leading to an exaggerated degree of local oxygen consumption. Prolonged infusions of epinephrine cause regularly anoxic necroses of cardiac muscle (Veith⁷⁰ and others).

Abnormally high concentrations either of the total adrenocortical compounds or of epinephrine alone have been found in the myocardium of persons who died from chronic or acute heart failure (Raab⁷¹).

As far as the relation between adrenocortical compounds and blood pressure is concerned, my findings do not furnish any evidence of a hormonal hemodynamic mechanism of essential hypertension. Both the complete absence of abnormally high levels of adrenocortical compounds in this condition and the general lack of correlation between elevations of the adrenocortical compounds and increases in the blood pressure after muscular exercise in normal persons also make it improbable that acute vasoconstrictor effects of the adrenocortical compounds play a predominant role in the mechanism of essential hypertension. Results of the experiments by Rogoff and Coombs⁷² demonstrating the insignificance of the adrenal glands in the mechanism of centrogenous hypertension through artificial reduction of the cerebral blood supply seem to support this view. However, it is possible that an acute local formation of epinephrine in the arterial walls by adrenergic neurons under the influence of sympathetic stimuli (Cannon and Lissák²⁷) and enhancement of its vasoconstrictor effects by locally deposited cortical sterols (Raab¹⁴) may contribute to abnormal elevations of the blood pressure.

Finally, in consideration of the outstanding pathogenic role of cerebral and renal arteriolosclerosis in arterial hypertension, the significance of secretion of adrenocortical compounds by the adrenal glands has to be considered also from the point of view of its effects on the

68. Gremels, H.: Ueber Potentialstoffe, *Ergebn. d. Physiol.* **42**:53-106, 1939; *Zur Physiologie und Pharmakologie des Säugetierherzens*, *Arch. f. exper. Path. u. Pharmacol.* **169**:689-723, 1933; Ueber die Steuerung der energetischen Vorgänge am Säugetierherzen, *ibid.* **182**:1-54, 1936.

69. Gollwitzer-Meier, K.: Die Energetik des Säugetierherzens, *Klin. Wchnschr.* **18**:225-231, 1939.

70. Veith, G.: Experimentelle Untersuchungen zur Wirkung von Adrenalin auf den Herzmuskel, *Arch. f. Kreislaufforsch.* **6**:335, 1940.

71. Raab, W.: (a) Hormonal Factors in the Origin of Heart Damage and Failure, to be published; (b) footnote 26.

72. Rogoff, J. M., and Coombs, H. C.: Observations on the Supposed Relation of the Adrenal Glands to the Blood Pressure Response During Cerebral Anemia, *Am. J. Physiol.* **64**:44-74, 1923.

slow development of structural changes of the vascular walls, and not of its immediate vasoconstrictor effects alone.

There exists an extensive literature concerning the detrimental influence of hyperactivity of the adrenal glands (both of the cortex and of the medulla) on the arterial and the arteriolar walls (Raab ^{71a}).

Abnormally intense discharge of adrenocortical compounds into the blood stream after muscular exercise, such as occurred in many of my patients with essential hypertension, indicates that a general secretory hyperreactivity and a jerky mode of secretion of the adrenal glands are constitutional peculiarities of persons with hypertension. Since the presence of adrenocortical compounds in the tissue of human arterial walls could be demonstrated (Raab ²⁶), it seems reasonable to assume that these frequent discharges of adrenocortical compounds contribute to the development of those anatomic vascular changes in the brain and kidneys which eventually produce local ischemia and resulting elevation of the blood pressure, of a central or of a renal type or of both. The hypertrophy of the musculature of the adrenal veins, characteristic of persons with hypertension (Goldzieher and Sherman,⁹ Allen ¹⁰), may be a factor in the temporary retention and sudden, jerky discharge of large amounts of adrenocortical compounds from the adrenal glands.

The striking increase in the colorimetric readings on the blood of patients with extensive renal involvement, particularly those in the advanced stages of uremia, raised the question whether substances other than the adrenocortical compounds contribute to these high figures. For this reason a number of substances which are known or believed to be abnormally increased in the blood of uremic patients were tested in regard to their ability to give a color reaction similar to that of epinephrine and cortical sterols and also with respect to their adsorbability by aluminum hydroxide, a property which is indispensable for their participation in the final colorimetric results. Moreover, those substances which gave a positive color reaction but proved not to be adsorbable by aluminum hydroxide at a p_H of either 4.0 or 8.5 were added to fresh blood in high concentrations in order to check on the possibility that they might somehow become adsorbable and disturbing through contact with blood. The results (table 9) make it seem impossible that any of the enumerated nitrogenous and phenolic compounds interfere with the results obtained on the blood of patients with renal insufficiency. The specific ratio of the adrenocortical compounds in the blood of such persons did not suggest that epinephrine constituted a high proportion of their volume.

Although definite evidence cannot as yet be given for this assumption, it seems most likely that the presence of excessive amounts of adrenal hormonal compounds, particularly of sterols, in the blood of

uremic patients is due to an abnormal retention of these substances, which would otherwise be partly excreted in the urine.

The kidneys of the rat were found to store considerable amounts of parenterally injected epinephrine hydrochloride and desoxycorticosterone acetate (Raab⁵⁷), and trophic effects of gonadal hormonal sterols on the kidney were recently described by Korenchevsky and Ross⁷⁴ and by Selye.⁷⁵

The phenomenon of a pathologic sterolemia in persons with renal insufficiency requires further study. One interesting feature is the presence of severe electrocardiographic and myocardial changes in most patients with abnormally high levels of adrenocortical compounds

TABLE 9.—*Colorimetric Behavior of Substances Which Are or Possibly May Be Increased in the Blood of Patients with Renal Insufficiency*

Substance Examined	Color Intensity in Comparison with That of Epinephrine	Specific Ratio	Adsorbability by Aluminum Hydroxide at a pH of		Adsorbability After Mixture with Fresh Human Blood
			3.5-4.0	8.5	
Urea.....	0
Uric acid.....	1/300	1:1.3	0	0	0
Creatinine.....	0
Aminoacetic acid.....	0
Leucine.....					
Tyrosine.....					
Tyramine.....					
Cysteine.....					
Histidine.....					
Histamine.....					
Guanidine hydrochloride.....	0
Phenol.....	0
Indole.....	1/76	1:1.0	0	0	0
Skatole.....	1/143	1:1.0	0	0	0
Paracresol.....	1/5,000	1:2.0	0	0	..

in the blood. The influence of these substances on formation of edema and analogous abnormalities of water metabolism in advanced forms of renal disease may be significant.

In 3 young men with a moderately developed Cushing syndrome, who are not included in the tables, the level of adrenocortical compounds in the blood was found to be close to the maximal upper limit of normal (200, 220, 227 color units per cubic centimeter, respectively). These patients, 19, 17 and 21 years old, were obese and had marked purplish striae and moderately elevated blood pressures (144, 158 and

73. Deleted by author.

74. Korenchevsky, V., and Ross, M. A.: Kidneys and Sex Hormones, Brit. M. J. **1**:645-648, 1940.

75. Selye, H.: Effect of Testosterone on Kidney, J. Urol. **42**:637-641, 1939.

145 mm. of mercury systolic and 90, 78 and 90 mm. diastolic, respectively). Increased amounts of adrenal cortical substances have been found by Anderson and Haymaker⁷⁶ and by Fraser and co-workers⁷⁷ in the blood and urine of patients with Cushing's syndrome. The amount of corticotropic hormone of the anterior lobe of the pituitary body is increased in the blood of patients with essential hypertension, according to Jores.²⁰ These and other observations (Kylin⁷⁸ and others) support the view that a corticotropic hyperactivity of the anterior lobe of the pituitary body forms the pathogenetic background for the development of high blood pressure levels, not only in Cushing's syndrome but in other forms of hypertensive disease.

SUMMARY AND CONCLUSIONS

Human blood contains adrenal hormonal compounds consisting of epinephrine and cortical sterols (adrenocortical compounds).

Most of the normal persons with a level of adrenocortical compounds within the normal range, but above the average, were smokers.

Muscular exercise caused little change in the level of adrenocortical compounds in the blood of normal persons.

In patients with essential hypertension the resting level of adrenocortical compounds was normal, but it was usually found to be markedly elevated for a few minutes after physical exercise.

An abnormally high level of adrenocortical compounds was found in the blood of a number of patients with renal hypertension (1 of them 2 years of age), with congestive heart failure and associated pulmonary edema, and particularly in patients with renal insufficiency and associated uremia. In 3 patients with Cushing's syndrome the level was near the upper limit of normal.

No clear relation existed between the level of the adrenocortical compounds in the blood and the level of the blood pressure.

It is concluded that there is a tendency toward a jerky mode of secretion of the adrenal glands in persons with essential hypertension, which can be elicited by physical exercise, and probably by other stimuli. This phenomenon is believed to further the development of arteriolo-

76. Anderson, E., and Haymaker, W.: Adrenal Cortical Hormone (Cortin) in Blood and Urine of Patients with Cushing's Disease, *Proc. Soc. Exper. Biol. & Med.* **38**:610-613, 1938.

77. Fraser, R. W.; Forbes, A. P.; Albright, F.; Sulkowitch, H., and Reifenshtein, E. C., Jr.: Colorimetric Assay of 17-Ketosteroids in Urine, *J. Clin. Endocrinol.* **1**:234-256, 1941.

78. Kylin, E.: *Der Blutdruck des Menschen*, Dresden, Theodor Steinkopff, 1937.

sclerosis and resulting ischemia in the vasomotor centers of the brain and in the kidneys, thus contributing to the two outstanding mechanisms of common (central and renal) hypertension. Also, a damaging influence of adrenocortical compounds on the cardiac muscle appears probable, in view of the tendency of the myocardium to absorb and to deposit both epinephrine and cortical sterols. This harmful effect on the heart is particularly obvious in the case of severe renal insufficiency, with its excessive concentration of adrenocortical compounds in the blood.

The origin of the latter and its significance for certain features of the uremic syndrome require further study.

DETERMINATION OF UROBILINOGEN IN FECES AND IN URINE

A COMPARISON OF THE SPARKMAN AND THE WATSON PROCEDURE

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AND

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MINNEAPOLIS

Attempts to simplify and render more exact the methods available for estimating urobilinogen can meet only with approval. The difficulties inherent in the problem of determining this substance have prevented any method yet described from being more than roughly quantitative. The modification of Terwen's method which one of us (C. J. W.) has employed¹ is admittedly not an exact procedure, but it was shown to recover added amounts of crystalline mesobilirubinogen and stercobilinogen with satisfactory limits of error; in addition, it has yielded consistent results in clinical work.² This method provides for concentration, if necessary, of small amounts of urobilinogen from relatively large amounts of material, for instance, from grossly acholic feces, which may contain small but significant amounts of the substance. The same is true of relatively dilute urine containing urobilinogen in low concentration.

The method requires a four day collection of feces, and the average per diem amount of urobilinogen for this period is determined. This is regarded as essential, for the following reasons: 1. In studying the rate of blood destruction, no satisfactory conclusions can be drawn from a determination carried out on a single stool. The variation in rate of bile flow, in rate of motion of the intestinal contents and in filling of the large bowel with feces, on which the reabsorption of urobilinogen and its enterohepatic circulation principally depend, and, finally, the variation in water content of the feces may be so considerable from day

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1. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Feces and Urine, *Am. J. Clin. Path.* 6:458 (Sept.) 1936.

2. Watson, C. J.: Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch. Int. Med.* 59:196 (Feb.) 1937; III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *ibid.* 59:206 (Feb.) 1937; footnote 1.

to day that a period of four days is believed the minimum over which the average per diem excretion can be determined. 2. In studying the degree of biliary obstruction, it is evident that if it is due to a stone in the common duct, a shift in position of the stone within the duct may alter the egress of bile from day to day, or, if the stone remains constant in position, the small amount of bile usually escaping into the duodenum may vary considerably in bilirubin content from day to day, or even from hour to hour. The latter occurrence, of course, will be reflected by considerable variations in the urobilinogen content of individual stools. In cases of parenchymal jaundice with marked, but not complete, cessation of bile flow, considerable variation may be noted from day to day in the amount of fecal urobilinogen. This is due either to variation in rate of bile flow or to varying concentration of bilirubin in the bile. In either case, determinations based on single specimens may provide entirely different information, and comparison of data is not possible on this basis. Much more reliable information might be obtained if individual determinations could be made on each specimen for several days, but the technical difficulties entailed eliminate this so far as routine purposes are concerned.

Complete biliary obstruction is present in over 90 per cent of cases of cancer of the biliary tract.³ In this group, of course, determinations made on individual stools will usually indicate the presence of complete obstruction, since, once established, this is most often constant and persistent. Occasionally, however, biliary obstruction is not complete, and single determinations may not indicate the state of affairs correctly. An example will be cited later.

Sparkman⁴ has recently advocated single determinations of urobilinogen on individual specimens of feces, expressing the content in milligrams per hundred grams. The amount in twenty-four hour specimens of urine is expressed in milligrams per hundred cubic centimeters. The method used by Sparkman does not provide for concentration of small amounts of urobilinogen from either feces or urine.

The purpose of the present study was to compare the Sparkman procedure with that described by one of us (C. J. W.).¹ We have had insuperable difficulty in making the color comparisons with the Spark-

3. Watson, C. J.: Regurgitation Jaundice: Clinical Differentiation of the Common Forms, with Particular Reference to the Degree of Biliary Obstruction, *J. A. M. A.* **114**:2427 (June 22) 1940.

4. Sparkman, R.: Studies of Urobilinogen: I. A Simple and Rapid Method for Quantitative Determination of Urobilinogen in Stool and Urine, *Arch. Int. Med.* **63**:857 (May) 1939; II. Normal Values for Excretion of Urobilinogen in Single Specimens of Urine and Stool, *ibid.* **63**:867 (May) 1939; III. Clinical Value of Determinations of Urobilinogen Content of Single Specimens of Urine and Stool, *ibid.* **63**:872 (May) 1939.

man method. The standard, which contains gold chloride, presumably to compensate for disturbing yellow colors from the urine or feces, is too yellow. Comparisons of samples with lesser concentrations of urobilinogen were found to be impossible. A rough estimation was possible with higher concentrations. In the following reports of determinations carried out on acholic feces containing significant small amounts of urobilinogen only qualitative descriptions are given, since color comparisons with the Sparkman standard were impossible.

COMPARISON OF RESULTS

Determinations of fecal and/or urinary excretion of urobilinogen were made on specimens collected from patients with various clinical conditions, as well as on normal specimens.

Primary Carcinoma of the Common Bile Duct (case 1).⁵—The case of A. H., a 65 year old man, may be summarized as follows:

The patient died of a primary carcinoma of the common bile duct. He had had mild attacks of biliary colic and occasional episodes of slight jaundice for five years and advanced jaundice for six months previous to his admission to the hospital. Pruritis and an enlarged liver were also noted at the time of examination. The diagnosis at the time of operation was cholelithiasis. The common bile duct was dilated, but the cause of obstruction was not ascertained. At necropsy an adenocarcinoma of the common duct was found just above the ampulla of Vater. The lesion, which measured 8 mm. in diameter and was situated on the posterior wall of the duct, was not ulcerating, but was obstructing the right half of the ampulla by pressure alone. The left half was apparently patent.

Results obtained with the two procedures under consideration are compared in table 1.

Catarrhal Jaundice (case 2).—The case of E. S., believed to be one of Eppinger's⁶ cholangitic type, may be summarized as follows:

The patient, aged 48, was admitted to the hospital on Nov. 1, 1939 with jaundice and pruritus, of five weeks' duration. Two weeks prior to admission he had felt pain in the right upper quadrant of the abdomen, dull, but not colicky and not radiating to the back. Vomiting occurred for several days prior to admission. The presence of deep jaundice, bilirubinuria and acholic stools was noted. The liver was enlarged, and its edge was palpable 10 cm. below the costal margin in the right midclavicular line. The spleen was palpable.

Pertinent laboratory data were as follows: Duodenal drainage after the installation of magnesium sulfate revealed numerous pus cells but no crystals. On November 4 the bromsulphalein test showed 60 per cent retention after half an hour (5 mg. per kilogram of body weight). On November 7 the levulose tolerance test showed

5. Dr. W. F. Hartfiel and Dr. J. F. Noble, of St. Paul, gave us permission to study this case.

6. Eppinger, H.: *Die Leberkrankheiten*, Berlin, Julius Springer, 1937.

104 mg. at the fasting level, 133 mg. one hour after 50 Gm. of levulose was administered and 133 mg. two hours after, with a combined rise of 58 mg. (upper limit of normal, 30 mg.). On November 11 the galactose tolerance test showed 1.8 Gm. per hundred cubic centimeters of urine after 40 Gm. of galactose was administered orally. On November 13 the stercobilin tolerance test showed 22 mg. excreted in the urine during the twenty-four hours following intravenous injection of 50 mg. of crystalline stercobilin (upper limit of normal, 5 mg.).

TABLE 1.—*Urobilinogen Findings During Life of a Patient with Primary Carcinoma of the Common Bile Duct*

Feces, Individual Samples		Method Used in Determining Urobilinogen	
Number	Weight in Gm.	Sparkman	Watson
1.....	97	Light red	2.32 mg. (total)
2.....	115	Pinkish red	3.79 mg. (total)
3.....	317	Pinkish red	3.89 mg. (total)
4.....	120	Yellow	1.02 mg. (total)
5.....	141	Pinkish yellow	29.60 mg. (total)
6.....	156	Yellow	7.10 mg. (total)
7.....	80	Yellow	1.50 mg. (total)
Entire 4 day specimen *.....	940	Pinkish yellow	17.10 mg. (total)
Urine, 24 hour specimen.....		Yellow	2.20 mg. (total)

* This included two small individual samples on which separate determinations were not made. Because of this and the fact that at least 10 Gm. had been removed from each of the seven individual specimens, the weight of the four day sample and the average per diem excretion of 17.1 mg. of urobilinogen per day did not correspond exactly with the individual values given.

TABLE 2.—*Relation Between Icteric Index and Fecal and Urinary Excretion of Urobilinogen*

Date	Icteric Index	Fecal Urobilinogen, Mg. per Day	Urinary Urobilinogen, Mg. per Day
11/ 5.....	..	6.6	0
11/ 7.....	69
11/13.....	125	10.2	0
11/17.....	..	Trace	..
11/21.....	76	24.2	..
11/22.....	66	Trace
11/26.....	..	124.7	..
11/29.....	Trace
12/ 2.....	46

The relation between the icteric index and the excretion of urobilinogen is recorded in table 2, and the values for excretion as determined by the two methods are compared in table 3.

Hemolytic Anemia (cases 3 through 8).—Fecal excretion of urobilinogen was determined in 6 cases of hemolytic anemia. The values obtained by both the Sparkman and the Watson procedure are recorded in table 4.

Excess Urobilinogen in Urine (cases 9 through 12).—Determination of urobilinogen present in twenty-four hour specimens of urine was made

by both the Sparkman and the Watson procedure. The values are recorded in table 4.

Normal Urine.—Crystalline stercobilin was added to normal urine, and its recovery (in terms of urobilinogen) was measured according to the two procedures under comparison.

Method: Seventy-five milligrams of stercobilin hydrochloride dissolved in 1 cc. of 95 per cent alcohol was added to a twenty-four hour

TABLE 3.—*Comparison of Excretion of Urobilinogen in Feces as Measured in Case 2 by the Sparkman and by the Watson Procedure (for a Four Day Period)*

Number	Weight, Gm.	Sparkman	Watson
1.....	655	Yellow	12.57 mg.
2.....	40	Yellow	1.35 mg.
3.....	913	Yellow	9.58 mg.
4.....	641	Yellow	15.4 mg.
Entire 4 day sample *.....	2,260	Yellow	10.2 mg.

* Less 10 Gm. from each of the four individual specimens and including a fifth specimen on which separate determinations were not made.

TABLE 4.—*Comparison of Results Obtained with the Sparkman and the Watson Procedure in Analyses for Urobilinogen*

Case Number	Sparkman Method, Mg per Day	Watson Method, Mg. per Day
Feces in Cases of Hemolytic Anemia		
3.....	98.0	786.0
4.....	Color comparison impossible	318.0
5.....	401.5	1,031.7
6.....	83.0	702.0
7.....	118.0	617.7
8.....	675.5	828.2
Twenty-Four Hour Specimens of Urine Containing Excessive Amounts of Urobilinogen		
9.....	4.14 (poor color match)	46.0
10.....	18.81	36.4
11.....	23.60	47.6
12.....	6.10	19.3

specimen of normal urine measuring 2,290 cc. The Sparkman and the Watson procedure were then applied to separate portions of the mixture. The native urobilinogen, which is negligible in amount in dilute normal urine, was disregarded.

Results: According to the Sparkman method the percentage of stercobilin recovered was 61.

$\frac{(S) 15}{(R) 16.7} \times 0.9$ (standard factor) = 2.016 mg. per hundred cubic centimeters

$2.016 \times 22.9 = 45.8$ mg., or 61 per cent recovery.

According to the Watson method the percentage of stercobilin recovered was 91.6.

$$\frac{100}{50} \times \frac{75}{10} \times 0.2 \times 22.9 = 68.7 \text{ mg., or 91.6 per cent recovery.}$$

COMMENT

From the foregoing results it is evident that the Sparkman procedure is not sufficiently sensitive in the detection of small but significant amounts of urobilinogen in either feces or urine. In case 1 it is seen that weak color reactions were obtained with the Sparkman method in some of the individual specimens of feces. In specimen 6, for instance, the reaction was negative, although the sample was found to contain 7.1 mg. with the Watson technic. The Sparkman reactions in case 1 when positive were too weak and indefinite to permit colorimetric determination. It was impossible to interpret them in favor of either complete or incomplete biliary obstruction. It will be noted that in 3 of the 7 individual specimens, the color reaction was yellow (negative). According to Sparkman, this would indicate complete obstruction, but, as already mentioned, an appreciable amount of urobilinogen was found in specimen 6 with the Watson method. It is impossible to interpret weak reactions, such as those encountered with the Sparkman method in specimens 1, 2 and 3. The traces of urobilinogen present in the feces in many instances of complete biliary obstruction are sufficient to produce weak qualitative Ehrlich reactions, especially if the feces are relatively concentrated.

We are unable to confirm Sparkman's conclusion that his technic yields higher values for urobilinogen in both feces and urine than does the Watson procedure. The present results are, in fact, quite the opposite. We can only assume that the high values reported by Sparkman depend on an error in colorimetric determination related to the yellow color of the standard solution. Variable concentration of the urine, and hence of its yellow pigment, contributes further to poor color comparison. These factors probably account for the values reported for normal urine, which are undoubtedly much too high, i. e., 5 to 20 mg. per twenty-four hours. In our experience, the color comparison in the case of normal urine has not been possible with the Sparkman method.

From what has been said in the foregoing comment about average per diem values, the conclusion should not be drawn that we believe the qualitative tests on individual urine samples to have no value. On the contrary, the simple qualitative test,¹ if employed serially or at frequent intervals, is often most helpful. In using the qualitative test, however,

one must always bear in mind that dilution may give rise to a negative result in the presence of a significant increase and, conversely, that concentration may unduly emphasize an insignificant amount.

SUMMARY AND CONCLUSIONS

Direct comparison has been made of the Sparkman and the Watson procedure for estimation of urobilinogen in feces and in urine.

Sparkman's report of higher values obtained with his technic, particularly as applied to urine, has not been confirmed. Opposite results were noted in the present investigation. Reasons for this discrepancy are discussed.

Evidence is presented which indicates the desirability of (*a*) obtaining an average per diem value for excreted urobilinogen, especially for fecal urobilinogen, over a period of several days, and (*b*) using a method which permits concentration of small amounts of urobilinogen whenever necessary because of low concentration in the sample.

DIRECT CULTIVATION OF BACTERIUM TULARENSE FROM HUMAN BLOOD DRAWN DURING LIFE AND AT AUTOPSY

REPORT OF THREE FATAL CASES OF TULAREMIA, WITH
BRIEF NOTES ON TWO OTHERS

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THE OCCURRENCE OF BACTEREMIA

The concept of invasion of the blood stream in tularemia is embodied in the name given to the disease by Francis,¹ who wrote: "The name tularemia is based upon the specific name *Bacterium tularense*, plus -aemia, from the Greek, and has reference to the presence of this bacterium in the blood." In early investigations direct proof of bacteremia was furnished by animal inoculation. Blood from a patient with "deer-fly fever" who ultimately recovered was injected into guinea pigs by Francis¹ (case 3) and was found to be infectious. Simpson² similarly recovered the organism in 1 nonfatal case (XI) and also in a rapidly fatal case in which the blood was taken on the day before death. Such observations have been amply confirmed by others who have demonstrated by guinea pig inoculation the presence of *B. tularense* in the blood in fatal cases, both during life³ and at autopsy.⁴

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1. Francis, E.: The Occurrence of Tularemia in Nature as a Disease of Man, Pub. Health Rep. **36**:1731 (July 29) 1921.

2. Simpson, W. M.: Tularemia: A Clinical and Pathological Study of Forty-Eight Non-Fatal Cases and One Rapidly Fatal Case Occurring in Dayton, Ohio, Ann. Int. Med. **1**:1007 (June) 1928.

3. Francis, E., and Callender, G. R.: Tularemia: The Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927. Foulger, M.; Glazer, A. M., and Foshay, L.: Tularemia: Report of a Case with Postmortem Observations and a Note on the Staining of *Bacterium Tularense* in Tissue Section, J. A. M. A. **98**: 951 (March 19) 1932. Bernstein, A.: Tularemia: Report of Three Fatal Cases with Autopsies, Arch. Int. Med. **56**:1117 (Dec.) 1935.

4. Palmer, H. D., and Hansmann, G. H.: Tularemia: Report of a Fulminating Case with Necropsy, J. A. M. A. **91**:236 (July 28) 1928. Bunker, C. W. O., and

(Footnote continued on next page)

THE DIRECT CULTIVATION OF *B. TULARENSE* FROM
HUMAN MATERIAL

From Abscesses and Body Fluids.—We have found relatively few reports of the isolation of *B. tularense* directly from human material on culture mediums. Simpson reported 2 cases² (15 and 19) in which infectious material was secured by scraping the walls of abscesses. Growth occurred in three days on dextrose-cystine-peptone-meat infusion agar enriched with 5 per cent human serum. Shaw and Hunnicutt⁵ likewise succeeded in cultivating the organism when pus from axillary abscesses in 2 cases was inoculated onto veal brain infusion-cystine-serum agar containing 1 per cent dextrose. Murphy⁶ reported the isolation of *B. tularense* from an epitrochlear abscess both by direct culture on cystine-blood agar plates and by guinea pig inoculation. Foshay and Meyer⁷ described a case in which the organism was twice cultured from fluid obtained by aspiration of an infected olecranon bursa. Culture of the fluid on cystine-blood-dextrose agar slants yielded a few colonies of *B. tularense* in forty-eight to seventy-two hours. Gudger⁸ described a case in which the organism was recovered "in pure culture" from the pleural fluid during life and from the blood at autopsy but did not state whether the isolation was accomplished by direct cultivation or by means of animal inoculation. In a recent publication Foshay⁹ (page 44) mentioned another case, in which the organism was isolated by culture of ascitic fluid.

From the Blood.—A search of the literature has revealed only a few cases in which the direct isolation of *B. tularense* by culture from the blood of man has been reported. Sante¹⁰ described a nonfatal case of tularemia in which "culture of pus from the wounds of the fingers and from the blood, on brain-heart infusion and on brain-veal

Smith, E. E.: Tularemia: Report of Four Cases, One Fatal, with Autopsy Report, U. S. Nav. M. Bull. **26**:901 (Oct.) 1928. Archer, V. W.; Blackford, S. D., and Wissler, J. E.: Pulmonary Manifestations in Human Tularemia: A Roentgenologic Study Based on Thirty-Four Unselected Cases, J. A. M. A. **104**:895 (March 16) 1935.

5. Shaw, F. W., and Hunnicutt, T.: Direct Isolation of Bact. Tularense from Axillary Abscesses, J. Lab. & Clin. Med. **16**:46 (Oct.) 1930.

6. Murphy, J. L.: Tularemia in Michigan: Report of a Case, J. Michigan M. Soc. **29**:917 (Dec.) 1930.

7. Foshay, L., and Mayer, O. B.: The Viability of Bacterium Tularense in Human Tissues, J. A. M. A. **106**:2141 (June 20) 1936.

8. Gudger, J. R.: Tularemic Pneumonia: Report of a Fatal Case, J. A. M. A. **101**:1148 (Oct. 7) 1933.

9. Foshay, L.: Tularemia: A Summary of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in Six Hundred Patients, Medicine **19**:1 (Feb.) 1940.

10. Sante, L. R.: Pulmonary Infection in Tularemia: Case Report, Am. J. Roentgenol. **25**:241 (Feb.) 1931.

agar showed small aerobic, gram-negative, non-spore bearing, non-motile bacilli," which produced acid in dextrose-containing mediums. Graham¹¹ reported a case with survival in which one out of three blood cultures yielded a "Gram-negative organism resembling *B. tularense* morphologically." Neither of these two authors reported specific agglutination or animal inoculation tests with the isolated organisms reported, and Graham did not mention the type of medium which he employed.

Gundry and Warner¹² discussed a fatal case in which blood taken on the day before death was inoculated into dextrose broth and veal brain broth, the latter containing calcium carbonate. Growth was reported in both, being heavier in the veal brain broth and consisting of an organism "morphologically identical with *B. tularense*." A guinea pig inoculated intraperitoneally with 2 cc. of the original veal brain broth culture died in six days and showed "typical tularemic lesions" at autopsy. Transfers on culture mediums from the original blood culture were not described. Lufkin and Evenson¹³ reported another fatal case in which blood taken five days before death and inoculated into 0.3 per cent dextrose beef broth (p_H 7.4) yielded growth in seven days. A guinea pig which received an injection from the original blood culture died in four days with lesions described as typical of tularemia. Transfers from the guinea pig tissues and from the original blood culture broth were successfully made on cystine agar. Successive subcultures from the original blood culture were also reported to have grown well in dextrose broth until discarded. Neither Gundry and Warner nor Lufkin and Evenson reported specific agglutination tests with the organisms which they recovered.

Steele¹⁴ mentioned having obtained positive blood cultures on blood-dextrose agar from patients with tularemia, but details of identification were not described. Foshay⁹ (page 47) briefly discussed 2 cases of fatal septicemia in which heavy growths of *B. tularense* were isolated from blood taken during life and inoculated on to blood-dextrose-cystine agar slants.

MATERIAL

The material for the present study was supplied by 3 fatal cases of tularemia in which autopsies were performed at the Johns Hopkins Hospital, 1 each in December of the years 1937, 1938 and 1939, and

11. Graham, W. R.: Tularemia from Wood Tick Bite: A Case Report, in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 758.

12. Gundry, L. P., and Warner, C. G.: Fatal Tularemia: Review of Autopsied Cases with Report of Fatal Case, *Ann. Int. Med.* **7**:837 (Jan.) 1934.

13. Lufkin, N. H., and Evenson, B. A.: Tularemia Diagnosed by "Routine Blood Culture," *J. Lab. & Clin. Med.* **22**:346 (Jan.) 1937.

14. Steele, P. A.: Tularemia, *Illinois M. J.* **76**:156 (Aug.) 1939.

2 cases in which the patients died at Vanderbilt University Hospital in 1940. A brief summary of the bacteriologic work performed in 2 other fatal and 25 nonfatal cases of tularemia at the Johns Hopkins Hospital is included in the section on "Comment."

REPORT OF CASES

CASE 1.—History.—The past history of E. M., a 59 year old Negress, was not significant, except that for the last four or five years she had suffered from ankylosis and discharging sinuses of the right knee but had continued ambulatory. Otherwise she had been well until about ten days before admission, when she bought a rabbit and prepared it for her family. Later she noticed a sore on the left ring finger, and at the same time the glands in the left axilla became swollen and tender. Four days prior to admission she complained of weakness and went to bed. There were no chills, but she felt warm and feverish. Her condition became worse, and on Nov. 27, 1939, she was brought to the Johns Hopkins Hospital.

Physical Examination.—The patient was well developed and well nourished. Her rectal temperature was 104 F., pulse rate 100, respiratory rate 24 and blood pressure 120 systolic and 60 diastolic. She appeared acutely ill, toxic and dehydrated and was extremely drowsy. On the left ring finger there was a small pustule surrounded by minimal redness and induration. It was fluctuant and tender. A left epitrochlear lymph node was palpable, and there was a tender gland in the left axilla, measuring about 3 cm. in diameter. Questionable slight relative dullness and diminished breathing were noted at the base of the right lung. The heart beat was relatively slow and regular. The right knee was ankylosed, swollen, red and indurated and presented several small sinus openings discharging sanguinopurulent fluid. The remainder of the examination showed nothing abnormal.

Course.—On the day the patient was admitted to the hospital the pustule on the finger was incised, and on the second day of hospitalization the first of nine intravenous injections of commercial antitularenseserum^{14a} (totaling 119 cc. in forty-eight hours) was given. There was a high, unremitting fever, the temperature ranging from 103 to 105 F., with relative bradycardia. The stupor deepened, the pulse rate quickened and on the fifth day the leukocyte count rose abruptly to 25,000. Therapy with sulfanilamide was started, but death occurred on the following day, the patient's sixth day in the hospital. Because the day of onset is not definitely known the exact duration of the patient's illness cannot be stated, but it was probably between ten and fifteen days.

Pertinent Laboratory Data.—At the time the patient was admitted to the hospital examination of the blood showed the hemoglobin concentration to be 7.6 Gm. per hundred cubic centimeters (52 per cent), the erythrocyte count 3,320,000 per cubic millimeter, the leukocyte count 8,000 per cubic millimeter, with 40 per cent adult polymorphonuclears, 18 per cent juvenile polymorphonuclears, 18 per cent lymphocytes and 24 per cent mononuclears, and the reaction to the flocculation test for syphilis (Eagle) negative. Urine obtained by catheterization was normal except for a trace of albumin and acetone and a few erythrocytes and leukocytes. Roentgen examination of the chest showed the lungs apparently to be clear.

14a. The serum was obtained from the Mulford Colloid Laboratories, Philadelphia.

In the bacteriologic studies (Dr. Russell A. Nelson), pus taken on the first day of hospitalization from the lesion on the finger yielded no growth on blood agar or in cooked meat medium, but a moderate growth of *B. tularense* appeared in two days on blood-dextrose-cystine agar.

Cultures of blood made on the first, third and fifth days of hospitalization showed no growth on plain agar pour plates or in dextrose broth. Those made on the third and fifth days showed a moderate growth of *B. tularense* in ten days on blood-dextrose-cystine agar.

Agglutination tests performed on the second day of hospitalization gave negative reactions with *Eberthella typhosa*, *Salmonella suipestifer*, *Brucella abortus* and *Salmonella Schottmülleri* antigens, and a positive reaction in a dilution of 1:320 with *Salmonella paratyphi* antigen. Tests performed on the third day gave negative reactions with *E. typhosa* H and *B. tularense* antigens, and a weakly positive one with *E. typhosa* O antigen in a dilution of 1:40.

Cultures of stools made on the second and third days of hospitalization were negative for the typhoid-dysentery group of bacilli.

Clinical Diagnosis.—The clinical diagnosis was tularemia and tuberculous osteoarthritis of the right knee.

Pathologic Diagnosis (Dr. M. M. Ravitch).—The diagnosis made at autopsy included: tularemia, with the primary focus an ulcer on the left ring finger; suppurative inflammation of the epitrochlear and axillary lymph nodes on the left side; miliary abscesses of the liver, spleen and lungs; bilateral hematomas of the rectus abdominis muscle, and tuberculous osteoarthritis of the right knee, which was secondarily infected and showed a draining sinus.

Bacteriologic Studies After Autopsy.—Culture of heart blood yielded 10 to 15 colonies of *B. tularense* on a blood-dextrose-cystine agar slant after seven days' incubation. A similar slant incubated in 10 per cent carbon dioxide showed no growth. Culture of peritoneal fluid yielded 6 colonies of *B. tularense* on a blood-dextrose-cystine agar slant after three days' incubation in 10 per cent carbon dioxide. No growth occurred on a similar slant incubated aerobically. Neither pleural fluid nor pus from lymph glands showed growth on blood-dextrose-cystine agar incubated or in 10 per cent carbon dioxide.

CASE 2.—History.—J. L., a white laborer aged 52, was admitted to the Johns Hopkins Hospital on Jan. 13, 1938, complaining of chills and fever. His past history was not significant, except for chronic alcoholism, slight dyspnea on exertion, edema of the ankles and a chronic winter cough which had persisted for ten or more years. The diet had been inadequate, and he had lost 40 pounds (18.1 Kg.) in the past year.

The present illness began four days before his admission to the hospital with a severe shaking chill of about ten minutes' duration. Such chills recurred daily. He also suffered from constant aches in various joints and in the back, and there was marked prostration. It was learned that during the preceding month he had repeatedly skinned rabbits and that "two or three weeks" before admission he had an open sore on the right hand.

Physical Examination.—The patient appeared acutely ill. His temperature was 104.8 F., pulse rate 108, respiratory rate 28 and blood pressure 118 systolic and 72 diastolic. He was heavy-set and showed some evidence of recent loss in weight. No cutaneous lesions were detected. An enlarged lymph node was found in the right axilla, but there was no other lymphadenopathy. The tongue showed papillary atrophy. The chest was of emphysematous type, and a few dry rhonchi

were heard. Percussion suggested slight cardiac enlargement. At the apex an occasional third sound was noted, but there were no murmurs. The hepatic dulness was detectable by percussion 1 cm. below the costal margin, and the tip of the spleen was palpable. The remainder of the examination was noncontributory.

Course.—During the first few days of hospitalization the patient had an unremitting fever, the temperature ranging from 103.5 to 105 F., with relative bradycardia. He was irrational at times and gradually sank into stupor. The heart beat became irregular, with frequent premature contractions and episodes of trigeminal rhythm. On the eighth day of illness a few pinkish macules appeared on the flanks and abdomen. Two days later coarse rales were heard at the base of the right lung, and the pulse rate and respiratory rate became more rapid. The temperature rose to 108 F., and death occurred on the twelfth day of the disease.

Pertinent Laboratory Data.—At the time the patient was admitted to the hospital, examination of the blood showed the hemoglobin concentration to be 14 Gm. per hundred cubic centimeters (98 per cent), the erythrocyte count 5,100,000 per cubic millimeter, the leukocyte count 8,160, with 57 per cent adult polymorphonuclears, 32 per cent juvenile polymorphonuclears, 6 per cent lymphocytes, 4 per cent mononuclears and 1 per cent eosinophils, and the reaction to the flocculation test for syphilis (Eagle) negative. Urine obtained by catheterization was normal, save for a trace of albumin. Later voided specimens showed persistent small amounts of albumin, a few leukocytes and erythrocytes and many granular casts. Culture of the spinal fluid yielded no growth of any organism. Roentgenograms of the chest made on the seventh day of illness suggested patchy consolidation in the upper lobe of the right lung.

Cultures of the blood made on the fifth, eighth and eleventh days of illness showed no growth on pour plates or in broth. *B. tularensis* was isolated on blood-dextrose-cystine agar slants in cultures made on the eighth and eleventh days. On the seventh day of illness 5 cc. of the patient's blood was inoculated intraperitoneally into each of 2 guinea pigs, both of which died three days later with lesions typical of tularemia. Agglutination tests consistently gave negative reactions with *E. typhosa* H, *E. typhosa* O, *S. suispestifer*, *Proteus* X-19 and *B. abortus* antigens. The reactions for *B. tularensis* were as follows: on the seventh day of illness, negative; on the twelfth day of illness, after death, positive (2 plus) in a dilution of 1:20 and (1 plus) in a dilution of 1:40. A culture of the sputum made on the eleventh day of illness showed a heavy growth of a hemolytic strain of *Staph. aureus*. Cultures of the stools were repeatedly negative for organisms of the typhoid-dysentery group.

Clinical Diagnosis.—(The results of the blood cultures had not been reported at the time the patient died.) The clinical diagnosis was tularemia (?) or typhus fever (?) or typhoid fever (?), chronic addiction to alcohol, chronic bronchitis and emphysema of the lungs.

Pathologic Diagnosis (Dr. Joseph McManus).—The diagnosis made at autopsy included: tularemia; necroses in the spleen, liver, vertebral bone marrow and mediastinal lymph nodes; acute splenic tumor; fatty change in the liver; acute bronchitis; slight lobular pneumonia; metaplasia of the epithelium of the pancreatic duct with dilatation of the duct and the acini; calcification of vessels, and cellular infiltrations in the myocardium.

Bacteriologic Studies After Autopsy.—A culture of heart blood showed a few colonies of *B. tularensis* after four days' incubation aerobically on a blood-dextrose-cystine agar slant. Culture of material from the right lung yielded a few colonies

of *B. tularensis* after four days' incubation aerobically on two blood-dextrose-cystine agar slants.

CASE 3.—History.—L. S., a 62 year old white housewife, was admitted to the Johns Hopkins Hospital on Dec. 1, 1939, in stupor. Her past history was unimportant, except for some dyspnea on slight exertion and continuous moderate edema of the ankles during the previous two years.

Ten days prior to admission she cut the middle finger of her right hand and shortly thereafter cleaned and prepared some rabbits. On the next day she had the first of several severe shaking chills, followed by fever, malaise, nausea and vomiting. Eight days before admission she complained of epigastric pain, anorexia and occipital headache. Chills and fever continued, associated with marked weakness, and she remained in bed. The finger became swollen, and a pustule developed at the site of the wound. For two days preceding admission she was given sulfanilamide. She became dizzy and confused and was then sent to the hospital.

Physical Examination.—Her rectal temperature was 104.2 F., pulse rate 100, respiratory rate 36 and blood pressure 140 systolic and 80 diastolic. She was obese and appeared critically ill, stuporous, disoriented, markedly dehydrated and somewhat cyanotic. On the right middle finger there was a shallow, ragged ulcer, 0.5 cm. in diameter, with little or no surrounding inflammation. A slightly tender right epitrochlear lymph node, about 3 cm. in diameter, was felt, and over it the skin was reddened and warm. There was no other lymphadenopathy. A large purpuric lesion, measuring about 5 cm. across, was present on the left shoulder. The tongue was dry; on its right margin and on the mucosa of the left cheek two small shallow ulcers were present. A few medium moist rales were heard at the bases of both lungs. The heart appeared slightly enlarged, but no murmurs were heard. The rhythm was regular, for the most part, occasionally being interrupted by premature contractions, sometimes with coupling. The abdomen was distended, and bladder dullness was detectable by percussion halfway to the umbilicus. No other significant findings were noted.

Course.—The fever was remittent, with associated relative bradycardia. Abdominal distention persisted, respiratory distress increased and stupor deepened. On the twelfth day of illness several more large purpuric lesions were noted on the buttocks and flanks. At this time the patient was given 55 cc. of antitularensis goat serum intravenously in three injections, and a few hours later, 550 cc. of citrated blood from a donor who had recovered from tularemia contracted eleven months previously. (At the time of the transfusion this donor's serum agglutinated *B. tularensis* in a titer of 1:1,280.) The temperature dropped from 105 to 101 F. by the following morning, but a few hours later, on the thirteenth day of illness, the patient suddenly died, having been in the hospital only sixty hours.

Pertinent Laboratory Data.—At the time of the patient's admission to the hospital, examination of the blood showed the hemoglobin concentration to be 13.8 Gm. per hundred cubic centimeters (95 per cent), the erythrocyte count 4,480,000 per cubic millimeter, the leukocyte count 9,200, the reaction to the flocculation test for syphilis (Eagle) negative and the content of free sulfanilamide in the blood 3.9 mg. per hundred cubic centimeters. A sample of urine obtained by catheterization was normal, save for a trace of albumin, a few erythrocytes and leukocytes and occasional hyaline and granular casts. Roentgenograms of the chest made on the thirteenth day of illness showed enlargement of the heart, secondary changes in the lungs and an area of consolidation in the upper lobe of the right lung. An electrocardiogram made on the eleventh day of illness showed low

voltage in all leads, left axis deviation and sinus tachycardia with numerous premature auricular contractions.

Cultures of blood were made when the patient was admitted to the hospital, but no growth occurred either on pour plates or in broth. Culture of the sputum made on the twelfth day of illness yielded a pure culture of a hemolytic strain of *Staph. aureus*. Agglutination tests performed on the eleventh day of illness gave reactions with *B. tularensis* which were positive (3 plus) in a dilution of 1:80, plus-minus (\pm) in a dilution of 1:160 and negative in a dilution of 1:320. On the twelfth day the reactions for *B. tularensis* were positive (1 plus)¹⁵ in a dilution of 1:640 and negative in a dilution of 1:1,280.

Clinical Diagnosis.—The clinical diagnosis was tularemia and ulcerative stomatitis.

Pathologic Diagnosis (Dr. John Hamilton).—The diagnosis at autopsy included: tularemia; an ulcer of the right second finger; enlargement of the epitrochlear and axillary lymph nodes on the right side; multiple minute abscesses in the liver and spleen; acute ulceration of the pharynx; bilateral lobar pneumonia, and hyperplasia of the marrow of the femur.

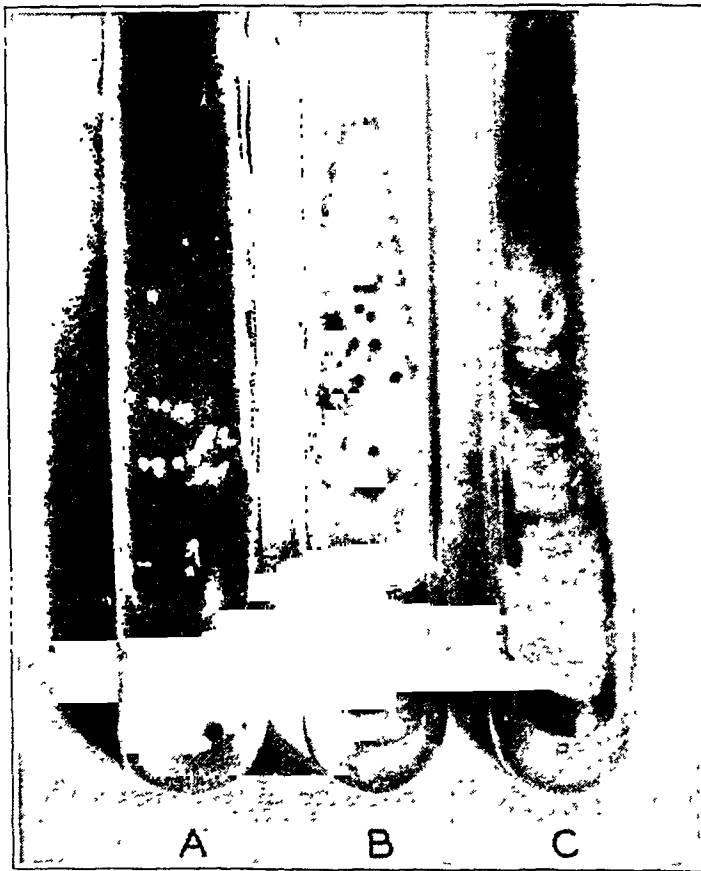
Bacteriologic Studies After Autopsy.—A culture of heart blood on one of three blood-dextrose-cystine agar slants showed 1 colony of *B. tularensis* after seven days' incubation aerobically. There was no growth on coagulated egg albumin or liquid sodium thioglycollate medium. Fifteen small colonies of *B. tularensis* were observed on one sodium thioglycollate-blood agar slant after eight days' incubation in air. No growth occurred on a second similar slant. *Staph. aureus* was isolated in cultures of material from the lungs.

CASE 4.—Recently one of us (J. C. R.) has had an opportunity for bacteriologic study of a fourth case of fatal tularemia which was observed in a ward of the Vanderbilt University Hospital. As this case is to be reported elsewhere by another author, only a brief note about it is included here. A 43 year old white farmer's wife entered the hospital in a prostrated and stuporous condition on the tenth day of a hectic illness characterized by chills, headache, vomiting, generalized body aches, cough, pleuritic pain on the left side, hemoptysis, dyspnea and distention. She had a massive pleural effusion on the left side, which was tapped on the twelfth day of illness. *B. tularensis* was isolated from the fluid thus obtained by direct culture on each of three blood-dextrose-cystine agar slants and also from heart blood of a mouse which died on the third day after being inoculated intraperitoneally with some of the same fluid. Blood cultures in dextrose broth and on dextrose and plain agar pour plates were negative on the tenth and fourteenth days of the patient's sickness. Culture of the blood on blood-dextrose-cystine agar slants showed no growth on the twelfth day. When cultures were again made at autopsy on the sixteenth day of the disease, *B. tularensis* was obtained in pure culture on two of three slants inoculated with 1 to 2 cc. of blood from the heart, the earliest colonies being observed after four days' incubation at 37 C. Antigen made from this organism gave agglutination to the full titer (1:10,240) of a known antitularensis serum, while being agglutinated in a dilution of only 1:80 by an antiabortus serum having a titer of 1:5,120.

CASE 5.—Another similar case of tularemia associated with pulmonary involvement, pleuritis and pleural effusion has since been observed at the Vanderbilt University Hospital. A 19 year old white girl, with no history of tick bites or

15. The blood for this test was drawn after the first injection of serum.

of contact with rabbits or other game, entered the hospital on the ninth day of illness; death occurred on the fifteenth day. Her serum agglutinated *B. tularensis* in a titer of 1:160 on the ninth day and 1:320 on the fourteenth day. There was no agglutination of *Br. abortus* antigen. Cultures of venous blood taken on the eleventh day of disease and of heart blood obtained at autopsy on the fifteenth day, inoculated as previously described onto blood-dextrose-cystine agar slants, were both positive for *B. tularensis*, while the organism was obtained in a similar manner from pleural fluid drawn on the twelfth day. This strain was likewise agglutinated by a known antitularensis serum to its full titer of 1:2,560, while cross agglutination occurred in a titer of only 1:20 with an antiabortus serum the titer of which with *Br. abortus* antigen was 1:20,480.



B. tularensis growing on blood-dextrose-cystine agar (case 5). *A*, culture made from venous blood four days before death (appearance after about ten days' incubation at 37 C.); *B*, culture made from pleural fluid three days before death (appearance after about six days' incubation); *C*, second transfer from *B* with growth after forty-eight hours.

Cultures obtained in case 5 are shown in the accompanying photograph. In the figure, *A* shows *B. tularensis* growing on a blood-dextrose-cystine agar slant inoculated with 1 cc. of the patient's blood taken on the eleventh day of illness, or four days before death, and incubated at 37 C. for about ten days. The first colonies were seen after six days. During the first five days the slant was tilted daily to allow the serum to flow over the surface of the medium. Part *B* shows a similar culture obtained from the pleural fluid on the twelfth day, and *C*, the appearance of the same organisms after two transfers on blood-dextrose-cystine

agar. In *B* note the confluent growth at the junction of fluid and agar, with numerous small, discrete colonies on the medium above. The colonies were round, moderately elevated, grayish, opaque and soft in consistency. In this culture they became visible after three days' incubation.

METHODS OF DIRECT ISOLATION USED IN THE PRESENT STUDY

From Clinical Material.—CASE 1.—Material from the pustule on the finger was obtained by incision and was inoculated directly onto slants of blood-dextrose-cystine agar. Moderate growth appeared in two days.

Cultures were made from blood taken by venipuncture from the arm. On the first occasion (the third day of hospitalization) 10 or 15 cc. of blood was introduced into about 6 cc. of a sterile 2.5 per cent solution of sodium citrate. One cubic centimeter of the citrated blood was then placed on each of several blood-dextrose-cystine agar slants. The second attempt was made on the fifth day by introducing 1 cc. of blood directly from the patient's vein onto the slants at the bedside. The tubes were tilted several times before coagulation occurred so that the blood was distributed over the entire surface of the medium. On both occasions growth of *B. tularensis* was observed in ten days.

CASE 2.—Venous blood from this patient was inoculated directly onto blood-dextrose-cystine agar slants on the eighth and eleventh days of his illness; 1 or 2 cc. per slant was used, as already described. On the first attempt only one round, grayish colony was obtained, and it reached a diameter of about 2 mm. in six or seven days. The second culture yielded a much heavier growth, which occurred chiefly at the junction of the surfaces of blood and agar in the form of small, gray-white colonies. Scattered colonies also appeared on the upper portions of the medium, and on one slant the growth was so heavy that it was almost confluent in places.

CASE 3.—Cultures were not made on blood-dextrose-cystine agar in this case during life because no medium was available at the time.

From Autopsy Material.—Material for culture was taken in the usual manner, by using sterile capillary pipets with rubber bulbs and by puncturing the organs through a small area of the surface which had been sterilized by searing with a hot iron. About 2 cc. of blood was usually obtained from the heart by this method, while only a drop or two of material could be gotten from the lung or spleen. Several cubic centimeters of fluid could generally be secured from the peritoneal cavity.

The original material thus obtained was placed immediately in a tube containing 5 or 6 cc. of infusion broth. Six or 8 drops of this broth suspension was introduced at the base of several blood-dextrose-cystine agar slants and allowed to flow over the surface of the medium. Each day during the period of incubation the tubes were tilted so that any fluid not absorbed by the medium could flow over the surface. This was to insure growth of the organisms on the solid medium and not solely in the fluid, where their presence might not be recognized, even in gram-stained smears of such fluid.

In cases 4 and 5 blood obtained in a syringe from the heart at autopsy was introduced directly onto the slants of blood-dextrose-cystine agar. In case 5 *Staph. aureus* was also present in the heart blood, 2 colonies being seen on the slant after twenty-four hours' incubation. Because of this the tube was not tilted, and on the third day several small colonies of *B. tularensis* appeared near the

upper level of the blood and were successfully picked, the entire slant being later completely overgrown with staphylococci. A second slant was overgrown from the start. Although successful in this instance, the method described is obviously a poor one to use if more rapidly growing organisms are present along with *B. tularense*. In such cases guinea pig inoculation is, of course, the method of choice.

Cultures were incubated at 37 C. for at least fourteen days. In cases 1 and 3 the first colonies were observed after seven days' incubation, while in case 2 growth was detected in four days. The number of colonies per slant varied from 1 to 15. On first appearance the colonies were tiny, gray and translucent, but on further incubation they became increasingly larger and more opaque.

Identification of Cultures.—Smears from the colonies obtained during life and at autopsy showed what at first glance appeared to be an undifferentiated mass of gram-negative material. Close study was necessary to distinguish individual organisms, which were extremely tiny and pleomorphic. Coccoid forms usually predominated, although sometimes many short bacillary forms were seen.

The organisms were identified as *B. tularense* by growth requirements and by agglutination tests with known antitularenses serum. All strains grew well on blood-dextrose-cystine agar and were transferred successfully at intervals of three to seven days for many generations. With one exception, no growth occurred on plain agar, blood agar or blood-dextrose agar. The organism isolated in case 1 during life at first failed to grow on these mediums but later grew poorly on blood-dextrose agar plates. The strain obtained from the same patient at autopsy grew, for one generation only, on a blood-dextrose agar slant.

In case 3 *B. tularense* was also isolated from heart blood on Brewer's sodium thioglycollate medium¹⁶ containing blood, dextrose and 2 per cent agar when slants of this medium were inoculated from the original broth suspension after twenty-four hours' incubation. This medium approximated blood-dextrose-cystine agar, except that sodium thioglycollate was substituted for the cystine. It was prepared by adding 2 per cent agar and 10 per cent blood to the sodium thioglycollate medium, which is available commercially in dehydrated form, both with and without methylthionine chloride (methylene blue). It seems important that the preparation without methylene blue be used, since small amounts of this substance appear to inhibit the growth of the organism.¹⁷ Brewer's liquid medium is designed to contain 0.1 per cent sodium thioglycollate and, when the dye is included, 0.0002 per cent methylene blue. The actual final concentration of these substances in the slants prepared as just described was somewhat less than this because of the addition of agar and blood. Three strains of *B. tularense* were maintained on such blood-dextrose-sodium thioglycollate slants for fourteen transfers over a period of thirty-three days without any perceptible decrease in the vigor of growth. Although satisfactory, the growth on this medium was never so luxuriant as it was on blood-dextrose-cystine agar.

16. Brewer, J. H.: Clear Liquid Mediums for the "Aerobic" Cultivation of Anaerobes. *J. A. M. A.* **115**:598 (Aug. 24) 1940.

17. Attempts to grow *B. tularense* on the dextrose-sodium thioglycollate-blood agar slants containing methylene blue were unsuccessful. To test the possible inhibitory action of the dye, blood-dextrose-cystine agar slants containing a similar final concentration of methylene blue were made. The initial growth on these slants seemed rather light, but after two or three transfers the usual vigorous growth was obtained.

All strains were agglutinated by antitularenses serum in a titer of at least 1:1,280. The antigen used for the agglutination tests was a suspension in a 0.9 per cent solution of sodium chloride of the organisms prepared by washing off the growth from young cultures on blood-dextrose-cystine agar slants. (For the protection of the laboratory worker either a solution of sodium chloride to which has been added solution of formaldehyde U. S. P. should be used in making the antigen or the suspension should be heated at 60 C. for one hour before the agglutination test is set up. If the solution of formaldehyde is used, enough should be added to the solution of sodium chloride to make a concentration of the former of 0.5 per cent, since solutions of lesser strength may fail to kill *B. tularenses* promptly. In addition, it is probably wise to allow the suspension treated with such a solution to stand for several hours before using in order to make sure that the bacteria are no longer viable. Killing the organisms by the solution of formaldehyde or by heat does not interfere with the results of the agglutination test.) Antitularenses diagnostic serum obtained from the National Institute of Health was used in some of the agglutination tests, and human serum of high titer from a patient proved to have had tularemia was used in the remainder. The organism obtained in case 2 during life was also agglutinated by serum obtained from patients with tularemia (who were in the hospital wards at the time) in a titer approximately equal to that secured with commercial *B. tularenses* antigen. Further confirmation of the identity of the cultures in case 2 was supplied when the worker (J. C. R.) engaged in preparing antigen from this strain contracted tularemia.¹⁸ The strain recovered at autopsy in case 3 was verified as *B. tularenses* by Dr. Edward Francis, of the National Institute of Health.

No difficulty was encountered in maintaining any of the strains of *B. tularenses* isolated. All those which were obtained at autopsy have been dried and preserved in vacuo, according to the method of Brown.¹⁹ Resuscitation of such dried cultures has been satisfactory.

COMMENT

In the files of the Johns Hopkins Hospital records of 30 proved cases of tularemia occurring in the years 1928-1939, inclusive, have been found. In 5 of these the disease was fatal, the mortality for the whole group being 16.6 per cent. This high death rate is probably explained by the fact that mildly ill patients are less apt to seek hospital

18. It seems likely that this case of laboratory infection was acquired by the handling of virulent cultures rather than infected animals. The person concerned did not touch the guinea pigs, and, although present at the autopsy on these animals (during which most rigorous precautions were observed), he did not perform it himself and did not become ill until three weeks later. It was during this interval that he was preparing antigen. He had no external lesion or lymphadenopathy, the disease being of the pulmonary type, terminating with recovery. The diagnosis was confirmed by a rise in the agglutinin titer from 0 on the tenth day to 1:10,240 on the thirtieth day.

A 0.9 per cent solution of sodium chloride to which was added solution of formaldehyde U. S. P. was used in making the suspensions for antigen. No recognized laboratory accident occurred to explain the means of infection, which remains a mystery.

19. Brown, J. H.: The Preservation of Bacteria in Vacuo, *J. Bact.* **39**:10 (Jan.) 1940.

care. The incidence of the various types of the disease encountered was as follows:

Type	Percentage of Total		
	Cases	No. of Cases	Deaths
Uncomplicated ulceroglandular.....	18	60.0	0
Uncomplicated oculoglandular.....	1	3.3	0
Pharyngeal glandular.....	2	6.6	0
Pulmonary only.....	3	9.9	0
Typhoidal (cryptogenic).....	2	6.6	1
Ulceroglandular and pulmonary.....	1	3.3	1
Ulceroglandular and typhoidal.....	3	9.9	3
Totals	30	—	5

On 18 of these patients a total of thirty "routine" blood cultures in infusion broth with or without dextrose and on plain and dextrose agar pour plates were made. All were reported negative for *B. tularense*. In the 5 fatal cases eleven "routine" blood cultures were made, none of which yielded growth, despite the fact that in 2 of these cases simultaneous cultures on blood-dextrose-cystine agar were positive for *B. tularense* and in 2 others tularemia developed in guinea pigs inoculated with the patient's blood. In 6 cases nine blood cultures were made on blood-dextrose-cystine agar, four of which were positive, two in each of 2 fatal cases here reported (cases 1 and 2). The remaining five cultures were made in 4 nonfatal cases, and all were negative. To recapitulate, *B. tularense* was cultured from the blood in only 2 cases during life, and growth was obtained each time only on blood-dextrose-cystine agar. In both of these cases the patients had an overwhelming "typhoidal" type of infection. The earliest positive blood cultures were made three and four days before death in cases 1 and 2, respectively.

Pus from suppurating glands was cultured thirteen times on blood agar or in broth and three times on blood-dextrose-cystine agar in 7 cases of the ulceroglandular type of the disease, but *B. tularense* was not recovered. Guinea pig inoculation with pus in 1 of these cases gave negative results on two occasions.

Cultures from the original local lesion were made seven times on blood agar or in broth and five times on blood-dextrose-cystine agar in 8 cases, and *B. tularense* was obtained only once, growth occurring on the cystine medium (case 1). Guinea pig inoculation from the initial lesion in 1 case gave a negative result.

In this series of cases cultures on "routine" mediums were always unsuccessful, while on some occasions growth was obtained on blood-dextrose-cystine agar inoculated simultaneously. In evaluating the results of cultures, the type and stage of the disease must of course be taken into consideration, so that a statistical summary such as the

foregoing is of limited value. It is well known, for example, that pus from suppurating glands is much more apt to yield *B. tularensis* if examined early, when the first signs of fluctuation appear. Likewise, one may expect a higher percentage of positive results if material from the local lesion is obtained during the pustular stage than if it is secured later, when ulceration has occurred and secondary infection may be present. Although it has been proved that bacteremia may occur in nonfatal cases,²⁰ the actual incidence of invasion of the blood stream in all types of human tularemia cannot be reliably estimated. Data on this subject are fragmentary, but we may conjecture that during the first week of the disease an initial bacteremia may occur, perhaps with some frequency, developing in cases of the fulminating type into an overwhelming septicemia. In those patients who die after a more prolonged course a secondary invasion of the blood stream prior to death is probably extremely common.⁹ It seems likely that if attempted on proper mediums, positive blood cultures could be obtained with some regularity from patients with tularemia who have a severe septicemic type of infection, particularly in the last stages of the disease.

Because of the extreme susceptibility of guinea pigs to tularemia, it is possible that the inoculation of infected material into these animals may remain the most reliable method of demonstrating the presence of *B. tularensis*. It has been suggested that the direct cultivation of the organism might entail less danger of infection among laboratory workers than does animal inoculation. Since one of the authors (J. C. R.) contracted tularemia, presumably from working with virulent cultures, it is our opinion that the cultivation of *B. tularensis* is not entirely safe.

Considering that the reliability of the agglutination test in tularemia has been well established,²² we recommend that when the presence of agglutinins, particularly in rising titer, permits a positive diagnosis, direct cultivation and animal inoculation be avoided by nonimmune workers. In cases of fulminating type in which death occurs before agglutinins have developed, the isolation of *B. tularensis* by direct cultivation may confirm the diagnosis, but the danger of this procedure should be recognized.

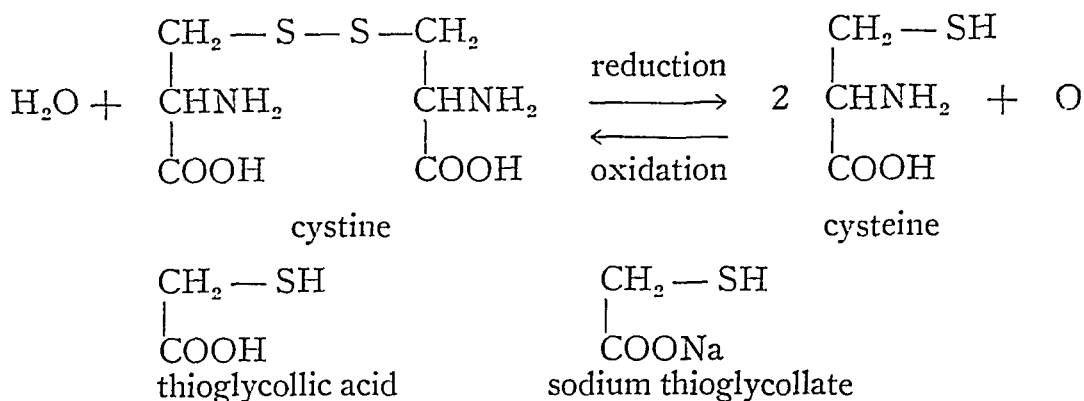
Except for identification of recently isolated cultures, antigen should never be made with virulent strains of *B. tularensis*. Relatively non-virulent strains which are entirely satisfactory for antigen can be obtained. Antigen should be killed by heat or a 0.5 per cent concentration of formaldehyde.

20. Francis.¹ Simpson.²

21. Footnote deleted by authors.

22. Francis, E., and Evans, A. C.: Agglutination, Cross Agglutination, and Agglutinin Absorption in Tularemia, Pub. Health Rep. **41**:1273 (June 25) 1926.

Sodium thioglycollate may be substituted for the cystine in blood-dextrose-cystine agar and will support the growth of *B. tularensis*. This is not surprising in view of the close chemical relation between these two sulfur-containing compounds. Thus, cystine may be reduced to cysteine, a substance differing from thioglycollic acid only in that the latter lacks the middle carbon atom with its attached $-\text{NH}_2$ group. These relations are shown in the following formulas²³:



Francis²⁴ has shown that substances containing potential or free $-\text{SH}$ groups, such as cystine, cysteine and glutathione, favor the growth of *B. tularensis*, while those containing sulfur in other forms are ineffective. It thus seems reasonable to suppose that it is the $-\text{SH}$ group in sodium thioglycollate which supplies the growth-promoting factor for *B. tularensis*. We have not carried out a careful quantitative study of this property of sodium thioglycollate. In our experiments more luxuriant growth was obtained with cystine, and as the cystine-containing medium has proved satisfactory during years of use,²⁵ we were not particularly interested in trying to perfect a new medium.

SUMMARY

Three fatal cases of tularemia are reported. *B. tularensis* was cultured directly on blood-dextrose-cystine agar from the blood in 2 of these cases during life and in all 3 at autopsy. In addition, the organism was cultured in case 1 from a pustule on a finger during life and from peritoneal fluid at autopsy, and in case 2 it was similarly recovered from the lung post mortem. Brief notes are included about 2 other fatal cases of tularemia, in 1 of which (case 4) *B. tularensis* was

23. Bodansky, M.: Introduction to Physiological Chemistry, ed. 3, New York, John Wiley & Sons, Inc., 1934, p. 306.

24. Francis, E.: Personal communication to the authors.

25. Francis, E.: Culture of Bacterium Tularensis on Three Additional Media New to This Organism, Pub. Health Rep. **37**:987 (April 28) 1922; The Amino-Acid Cystine in the Cultivation of Bacterium Tularensis, *ibid.* **38**:1396 (June 22) 1923.

recovered by direct culture and by mouse inoculation from pleural fluid taken during life and by direct culture from heart blood obtained at autopsy. In case 5 the organism was cultured directly from venous blood taken four days before death, from pleural fluid taken three days before death and from heart blood taken post mortem.

Bacterium tularense was also obtained by direct culture from heart blood in case 3 at autopsy by use of blood-dextrose-sodium thioglycollate medium without methylene blue.

Although three strains of *B. tularense* have been maintained through many transfers on this thioglycollate medium, the growth has not been so luxuriant as that obtained on blood-dextrose-cystine agar.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF LITERATURE FROM JULY 1940 TO JULY 1941

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A steadily increasing interest in a more complete understanding of the physiology of the gastrointestinal tract is evident in any review of the literature of recent years. Such a search for exact information reveals more and more the intricate interrelations that are involved in the processes of digestion. Accordingly, investigative technic has tended to become more and more complicated. At the same time, there can be little doubt that the result is a clearer understanding of the many mechanisms responsible for the proper functioning of the gastrointestinal tract and of the many possible causes of disturbances productive of symptoms.

During the past year numerous carefully controlled studies have been made on gastrointestinal physiology and some important information has been added to the literature. These studies have been concerned with the secretory, motor, absorptive and circulatory aspects of digestion. Contributions on the clinical aspects of disease affecting this system of the body are numerous and in many instances are merely repetitions of well or fairly well recognized facts. Certain articles, however, bring into stronger relief important clinical considerations and thus form valuable contributions to diagnostic and therapeutic knowledge. This is particularly true in regard to newer forms of chemotherapy and, to some extent, to the relation between deficiency conditions and digestive disturbances. The following review will attempt to present and comment on what are considered to be the more important or more interesting contributions of the past year.

PHYSIOLOGIC ASPECTS

A field as yet inadequately explored is that of the effect of age on digestive processes. Meyer and Necheles¹ have added to the studies

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1. Meyer, J., and Necheles, H.: Studies in Old Age: IV. The Clinical Significance of Salivary, Gastric and Pancreatic Secretion in the Aged, J. A. M. A. **115**:2050 (Dec. 14) 1940.

of Bloomfield and others by making observations on the changes in salivary, gastric and pancreatic secretion in older people. Moderate diminution in enzymatic activity of these digestive juices, except for that of amylase, was noted in the group under consideration. Such diminution apparently does not affect intestinal digestion, and despite the change in secretory activity under adequate stimulation the secretory mechanism is capable of response. These findings are entirely in keeping with the known fact that the secretion of gastric acid diminishes steadily in the later decades of life. The authors point out rather rationally, however, that restrictions imposed on old people because of fear of inadequate digestion of carbohydrate, protein and fat do not appear warranted. Actually, such restrictions may unnecessarily form the basis of the not too infrequent occurrence of deficiency states.

Among other studies on the still imperfectly understood mechanism of gastric secretion is that of Gray, Bucher and Harman² on the interrelation of total, acid and neutral chlorides of gastric juice. On the basis of a statistical analysis of data obtained from a large number of samples collected from dogs with vagotomized pouches of the entire stomach, it appears that after stimulation the output of total, acid and neutral chlorides increases in a linear fashion but at different rates. The more or less reciprocal relation between the concentration of total chloride and the concentration of neutral chloride is demonstrated. Brunschwig and his collaborators³ observed that radioactive chlorine ions passed readily from the blood into achlorhydric gastric juice. The relatively slow appearance of such ions would appear to be due to the smaller volume of gastric secretion obtained from a mucosa not capable of secreting free acid. Rasmussen and Brunschwig⁴ also demonstrated that the low pepsin content observed in patients with achlorhydria associated with carcinoma of the stomach is entirely comparable to that observed in other persons with achlorhydria but with no demonstrable organic disease.

A careful study of the acid-base balance, renal function and gastric secretion in 2 dogs during hypochloremia was made by Kirsner and Knowlton.⁵ Hypochloremia was produced by the withdrawal of

2. Gray, J. S.; Bucher, G. R., and Harman, H. H.: The Relationships Between Total, Acid, and Neutral Chlorides of Gastric Juice, *Am. J. Physiol.* **132**: 504, 1941.

3. Brunschwig, A.; Schmitz, R. L., and Slotin, L.: The Secretion of Chlorine Ions in Achlorhydric Gastric Juice: Observations by Means of Radioactive Chlorine, *Am. J. Digest. Dis.* **8**:171, 1941.

4. Rasmussen, R. A., and Brunschwig, A.: Peptic Activity of Achlorhydric Human Gastric Juices from Carcinomatous Stomachs: Comparative Study, *Proc. Soc. Exper. Biol. & Med.* **46**:298, 1941.

5. Kirsner, J. B., and Knowlton, K.: Acid-Base Balance, Renal Function, and Gastric Secretion During Hypochloremia in the Dog, *J. Clin. Investigation* **20**: 303, 1941.

histamine-stimulated gastric juice at two day intervals over periods of seventy-four to eighty-six days. The animals received a generous diet with added vitamins and a liberal allowance of chloride-free water. The intake of sodium chloride was maintained at a low level. At the end of the experimental period the serum chlorides of the 2 dogs had decreased to levels as low as 46.8 and 38.9 milliequivalents per liter, respectively. There was associated alkalosis, with a final p_H of 7.63 and 7.72, respectively. An approximate loss of 14 per cent of body weight was noted, and indirect evidence suggested that the blood sodium was diminished. Urea clearances were normal throughout the experiments, although excretion of ingested water was delayed as the chloride loss was intensified. Significant changes in hydrochloric acid secretion by the gastric mucosa were not obtained, in spite of the pronounced hypochloremia, and the alkalosis did not produce renal injury detectable either by the urea clearance test or by histologic examination, although some precipitation of calcium was observed in the renal collecting tubules. In other words, although the changes were of a magnitude that is rarely approached clinically in the absence of other evidence of malnutrition, it is obvious that even severe loss of chlorides, when gradual, probably does not produce alterations in body function and undoubtedly represents a condition which is easily reversible if proper replacement therapy is instituted.

A rather interesting study by Roth and Gabrielson⁶ is concerned with variations in gastric secretion following immersion of the hand or the entire body in water of various temperatures. Exposure to temperature well below that of the body appears to have resulted in a definite increase in gastric acidity, particularly after removal of the subject from the surrounding fluid. Exposure to water of body temperature or of temperatures as high as 42.2 C. caused little change, or even a slight decrease, and these investigators suggest that the rise in gastric acidity after exposure to temperatures of approximately 24 C. was probably due to the release of histamine or a histamine-like substance, inasmuch as histaminase introduced into the duodenum thirty minutes before immersion inhibited any increase. This inhibition by histaminase of histamine stimulation of gastric secretion is not corroborated by the observations of several other investigators. Necheles and Olson⁷ report the results of experiments on salivary, gastric, biliary and pancreatic secretion in animals and state flatly that the results do not lend

6. Roth, G. M., and Gabrielson, M. A.: Variation in the Concentration of Acids of the Gastric Content in Normal Subjects Before and Following Immersion of Hand and Entire Body in Water at Various Temperatures, *Am. J. Physiol.* **131**: 195, 1940.

7. Necheles, H., and Olson, W. H.: Histaminase: An Experimental Study, *Am. J. Digest. Dis.* **8**:217, 1941.

any support to the assumption that histaminase inhibits the response to histamine. Atkinson, Ivy and Bass,⁸ likewise on the basis of animal experiments, state that they have been unable to demonstrate that histaminase, given by any route, has a significant inhibitory effect on the gastric secretory response to the usual stimulating dose of histamine.

Palmer and his collaborators⁹ have carried out further studies on the gastric secretory curve in relation to "histamine-proved" achlorhydria. They emphasize the already demonstrated fact that such achlorhydria is not necessarily true anacidity and is not necessarily permanent, inasmuch as transient refractoriness to histamine may occur. Such findings do not at present explain the cause of this phenomenon, nor do they detract from the usual clinical deductions that may be drawn in certain conditions from the demonstration of achlorhydria after the administration of histamine, although the authors properly urge the necessity for careful technic before accepting the statement as to the existence of true anacidity.

The effect of parathyroid extract and of calcium on gastric secretion has been studied by several investigators. Babkin¹⁰ was able to show in dogs a diminished secretory response to various test meals and to histamine after single injections of parathyroid extract. After repeated injections, this response was intensified and there was only a gradual restoration to normal. In his experiments, the level of blood calcium remained normal throughout the entire period. He believes that the chief effect was on the nervous phase of gastric secretion. The prolonged administration of activated ergosterol had a similar effect, except that the gastric secretory response to histamine underwent little change. During the administration of activated ergosterol the blood calcium rose to about 15 mg. per hundred cubic centimeters.

Grant,¹¹ in animal experiments, noted that the intravenous injection of calcium salts inhibited gastric secretion and that the degree of inhibition seemed to depend more or less on the degree of hypercalcemia, inasmuch as sodium salts had no such effect. The result of hypercalcemia differed from the response to parathyroid extract or activated ergosterol, as noted by Babkin, in that it had no specific

8. Atkinson, A. J.; Ivy, A. C., and Bass, V.: The Effect of Histaminase on the Gastric Secretory Response to Histamine, *Am. J. Physiol.* **132**:51, 1941.

9. Palmer, W. L.; Kirsner, J. B., and Nutter, P. B.: Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation, *Am. J. Digest. Dis.* **7**: 427, 1940.

10. Babkin, B. P.: The Effect of Parathyroid Hormone and of Activated Ergosterol in Gastric Secretion in the Dog, *Rev. Gastroenterol.* **7**:373, 1940.

11. Grant, R.: The Inhibition of Gastric Secretion by the Intravenous Injection of Calcium Salts, *Am. J. Physiol.* **132**:460, 1941.

effect on the nervous or chemical responses of the gastric glands. The inhibitory process did not seem to depend on changes in osmotic pressure of the blood or on alterations in the gastric circulation. Further experiments¹² indicated that there was a reciprocal relation between the calcium concentration of the gastric secretion and the acidity, which could be demonstrated in connection with vagus and histamine stimulation. This relation was not dependent on volume changes but was interpreted as an index of the buffer value of the gastric juice, as expressed by the ratio of total acidity to free acidity.

The inhibitory effect of urogastrone on gastric secretion in man was studied further by Gray and associates.¹³ The previously noted inhibitory action was obtained after subcutaneous administration of a potent preparation of urogastrone, which reduced the gastric secretory response to histamine. The effect, however, was transitory, inasmuch as a subsequent injection of histamine sulfate, one-half hour after the administration of urogastrone, resulted in the usual secretory response.

In experiments on Pavlov pouch dogs, Komarov and Komarov¹⁴ noted a definite inhibition of gastric secretion after single or repeated doses of olive oil or cod liver oil. Olive oil inhibited gastric secretion more or less uniformly throughout the twenty-four hour period of observation, whereas there was some evidence that cod liver oil administered daily stimulated gastric secretion during the later hours of digestion and possibly exerted a cumulative effect.

Studies by Ehrenfeld and Sturtevant¹⁵ on the effect of smoking tobacco on gastric acidity showed that a definite increase in gastric acidity could be observed after smoking, as compared with control figures obtained on three fourths of a group of patients without gastrointestinal disturbances. Four out of 5 patients with ulcer showed a similar increase after smoking two cigarettes. In a small group of subjects, definite increases in acid values were observed after smoking popular brand cigarettes, whereas little or no change was noted when partially denicotinized cigarettes were used.

The influence of various fruit juices on gastric function was studied by Haggard and Greenberg.¹⁶ At the height of digestion there was no appreciable difference in the p_H of the gastric juice whether

12. Grant, R.: The Relation of Calcium Content to Acidity and Buffer Value of Gastric Secretions, *Am. J. Physiol.* **132**:467, 1941.

13. Gray, J. S.; Wieczorowski, E., and Ivy, A. C.: Inhibition of Gastric Secretion in Man with Urogastrone, *Am. J. Digest. Dis.* **7**:513, 1940.

14. Komarov, O., and Komarov, S. A.: The Effect of Olive Oil and of Cod Liver Oil on Gastric Secretion in the Dog, *Canad. M. A. J.* **43**:129, 1940.

15. Ehrenfeld, I., and Sturtevant, M.: The Effect of Smoking Tobacco on Gastric Acidity, *Am. J. M. Sc.* **201**:81, 1941.

16. Haggard, H. W., and Greenberg, L. A.: The Influence of Certain Fruit Juices on Gastric Function, *Am. J. Digest. Dis.* **8**:163, 1941.

water or fruit juices were given with a meal. Nor did the fruit juices exhibit any proteolytic activity. The emptying time of the stomach was slightly increased after the ingestion of fruit juices. Pineapple juice apparently caused a marked reduction in the emptying time of the stomach after meals containing protein or aminoacetic acid.

In view of the current attention to the use of gelatin in treating diseases of the stomach, the observations of Matzner and his associates¹⁷ are of some interest in confirming previous impressions that this substance tends to reduce the hydrogen ion concentration, free acid and pepsin in the gastric secretion. The tendency is due, undoubtedly, to the acid-combining power of the protein.

Advocates of meat extract as a suitable substance for routine test meals will find confirmation of their views in the observations of Fisher and Apperly,¹⁸ who demonstrated that test meals containing meat extract, in comparison with ordinary test meals, raise the concentration of total chlorides, free acid and pepsin in gastric juice and retard the dilution of the gastric contents. The authors suggest that meat extracts increase the appetite because of this stimulation and because of an associated increase in the tonicity of the gastric musculature.

On the basis of a rather ingenious series of experiments, Grindlay¹⁹ studied the secretion of gastric acid following operation on the distal end of the stomach. Fundic secretion appeared to be greatly increased when the pars pylorica was completely isolated from the remainder of the stomach. The author presents suggestive evidence that the pyloric portion of the stomach has an important relation to the chemical mechanism of gastric secretion. Complete isolation of the pars pylorica resulted in a striking and prolonged increase in the secretion of gastric acid, and the introduction of gastric contents into a completely isolated gastric (pyloric) pouch caused the fundic secretion during the second twelve hours after the feeding to be greater both in volume and in acidity than that occurring when gastric contents were not introduced. If such results obtained in animal experiments can be applied to human beings, it is obvious that simple surgical procedures directed toward exclusion only of the pyloric end of the stomach may be totally inadequate as far as control of gastric secretion is concerned and that the more radical procedures at present employed are more desirable and more efficacious.

17. Matzner, M. J.; Windwer, C.; Gawron, O., and Sobel, A. E.: Variations in the Composition of Gastric Juice, *J. Lab. & Clin. Med.* **26**:682, 1941.

18. Fisher, R. S., and Apperly, F. L.: Meat Extractives in Studies of Gastric Function, *J. Lab. & Clin. Med.* **26**:823, 1941.

19. Grindlay, J. H.: Studies on Secretion of Acid Following Procedures on the Distal End of the Stomach, *Am. J. Digest. Dis.* **8**:82, 1941.

The validity of deductions on the secretory activity of the stomach based on the dilution indicator technic with phenolsulfonphthalein is carefully discussed by Bandes, Hollander and Glickstein.²⁰ These authors point out, as have Wilhelmj and his co-workers, that erroneous figures are obtained both for human and for animal subjects by means of this technic, abnormally high figures having been frequently observed. These errors seem to be chiefly due to the absorption of fluid by the gastric mucosa in the presence of hypotonic test meals. When isotonic or hypertonic sodium chloride test meals are used, no such abnormally high figures are obtained. Bandes and his co-workers suggest that the use of isotonic test meals will minimize errors due to water absorption and may even eliminate them entirely.

The absorption of various substances by the gastric mucosa has formed the basis of various recent observations. Pratt,²¹ as a result of animal experiments, notes the absorption of sodium chloride and dextrose from solutions of these substances placed in the quiescent stomach. The amount absorbed increases with increasing concentrations. The administration of histamine tends to increase the amount of sodium chloride absorbed and to an even greater degree augments the amount of dextrose taken up at any initial concentration. He suggests that the inhibitory effect of hypertonic solutions of sodium chloride on the secretion of hydrochloric acid by the gastric mucosa is greater than that produced by solutions of dextrose of corresponding strength and that this variation may be due to the greater tendency of sodium chloride to be absorbed by the stomach. Myant²² made somewhat similar observations on the absorption of sodium sulfate by the stomach. A hypertonic solution of this salt in animals offers much less resistance to the secretion of hydrochloric acid stimulated by the administration of histamine than does a solution of sodium chloride or dextrose. As is the case with sodium chloride or dextrose, the administration of histamine increases the absorption of sodium sulfate, and the experiments seem to demonstrate that the favorable influence of histamine on the absorption of dissolved substances from the stomach is not confined to substances such as dextrose and sodium chloride, which are readily absorbed in the intestine, but extends to the divalent sulfate ion, which is not readily absorbed.

20. Bandes, J.; Hollander, F., and Glickstein, J.: The Effect of Fluid Absorption on the Dilution Indicator Technique of Gastric Analysis, *Am. J. Physiol.* **131**: 470, 1940.

21. Pratt, C. L. G.: The Influence of the Composition of the Gastric Content upon the Effect of Histamine, *J. Physiol.* **99**:154, 1940.

22. Myant, N. B.: The Influence of Histamine on the Absorption of Sodium Sulphate by the Stomach, *J. Physiol.* **99**:156, 1940.

Further studies on the absorption of dextrose by the stomach and various portions of the small intestine have been carried out by a number of investigators. Karr, Abbott, Hoffman and Miller,²³ in intubation experiments on human beings, studied the absorption of solutions of dextrose in concentrations varying from 5 to 50 per cent. A far greater proportion of the sugar in an ingested solution of dextrose was absorbed from the gastroduodenal region than from the jejunoileal portion. Also, the range of concentrations of dextrose absorbed from the cardia of the stomach to the upper part of the jejunum was from the concentration of the solution ingested to approximately 4 to 6 per cent. The maximum concentration at which solutions of dextrose enter the duodenum is usually 15 per cent or less, an indication of the dilution factor. Abbott and his collaborators²⁴ carried out further experiments of a similar nature, using a rather complicated apparatus which permitted the experimenters to maintain a constant flow of solution of known concentration into the duodenum and to recover all that was not absorbed. It was found that, as compared with other regions of the alimentary tract of equal length, the duodenum absorbed dextrose rapidly and at a rate that varied in the individual subject from day to day. Though as little as 6 Gm. per hour was absorbed from dilute solutions of dextrose, the maximum rate from solutions of the normally occurring concentration range was about 20 Gm. per hour. Further studies concerning the disappearance of dextrose from the stomach with the pylorus functioning, its disappearance from the stomach and duodenum as a unit and, finally, its disappearance with the pylorus mechanically closed were made by Abbott and associates²⁵ on normal human subjects. After concentrated solutions of dextrose were ingested, a certain amount was shown to have been absorbed into the gastric wall during the first short period of contact. The rate at which dextrose left the stomach was usually influenced by the volume and the concentration of the solution of dextrose ingested, although there was a marked variation in this gastroduodenal response to the ingestion of concentrated solutions in the same and in different subjects. It was demonstrated that the stomach and duodenum may often complete the absorption of dextrose without the aid of the small intestine.

23. Karr, W. G.; Abbott, W. O.; Hoffman, O. D., and Miller, T. G.: Intubation Studies of the Human Small Intestine: XIII. The Concentration and Movement of Glucose Solutions in the Stomach and Duodenum, *Am. J. M. Sc.* **200**: 524, 1940.

24. Abbott, W. O.; Karr, W. G.; Glenn, P. M., and Warren, R.: Intubation Studies of the Human Small Intestine: XIV. The Absorption of Glucose from the Duodenum, *Am. J. M. Sc.* **200**:532, 1940.

25. Warren, R.; Karr, W. G.; Hoffman, O. D., and Abbott W. O.: Intubation Studies of the Human Small Intestine: XV. The Absorption and Expulsion of Glucose from the Stomach, *Am. J. M. Sc.* **200**:639, 1940.

Somewhat similar studies were carried out by Shay and his co-workers,²⁶ who added to their previous observations on the subject. Using a four lumen tube and solutions of dextrose of various concentrations, the authors studied absorption at different levels in the small intestine. Although hypertonic solutions of dextrose decreased the rate of gastric emptying and thereby influenced absorption of dextrose, the authors feel that the human stomach is not the important diluting organ. The duodenum seems to possess a remarkable versatility in shifting from an absorptive organ for dextrose, when solutions of low concentration reach it from the stomach, to a diluting organ, when solutions of high concentration reach it. This change, of course, has been noted by various observers. The authors showed that the greatest absorption of dextrose from isotonic meals occurs in the duodenum and the jejunum, although, according to them, as the concentration of dextrose increases the absorption in these areas decreases proportionately. The explanation of Cori's conclusion that the rate of absorption of dextrose is independent both of the absolute amount and of the concentration of sugar in the intestine lies, the authors believe, in the retardation of gastric emptying and in the dilution mechanism of the duodenum resulting from hypertonic meals. The osmotic pressure of intestinal contents in fasting subjects was below isotonicity at all levels studied. After the administration of dextrose, the osmotic pressure in the duodenum appeared to depend on the concentration of the meal placed in the stomach, as below this level isotonicity was maintained, except in the lower portion of the ileum, where hypotonic conditions were found at practically all times. These observations led the authors to believe that absorption of water is greatest from the lower portion of the small intestine.

In attempting to determine the influence of adrenalectomy and of fasting on the intestinal absorption of carbohydrates, Marrazzi²⁷ showed that restriction of food intake or fasting seemed to account for the associated decrease in absorption of dextrose in adrenalectomized rats. He felt that anorexia alone probably could account for such a reduction in absorption of carbohydrates, inasmuch as the decrease in absorption of dextrose in animals subjected to sham operation was equivalent to that observed in those animals on which adrenalectomy was actually performed.

Studies on the rates of absorption of water and salts from the ileum in dogs with chronic Thiry-Vella ilea loops were carried out by Dennis

26. Shay, H.; Gershon-Cohen, J.; Fels, S. S., and Munro, F. L.: The Fate of Ingested Glucose Solutions of Various Concentrations at Different Levels of the Small Intestine, *Am. J. Digest. Dis.* **7**:456, 1940.

27. Marrazzi, R.: The Influence of Adrenalectomy and of Fasting on the Intestinal Absorption of Carbohydrates, *Am. J. Physiol.* **131**:36, 1940.

and Visscher.²⁸ Using solutions of sodium chloride and sodium sulfate, the authors conclude that the net absorption of solute is not equal to the calculated osmotic equivalent of water of the salt moved. The net effect, therefore, was absorption of a hypertonic solution. As to the mechanism involved, they feel that probably there is a two way movement, in which a hypertonic solution enters the intestine while salt solution leaves it to enter the blood. Thus they consider intestinal transport as the algebraic sum of two directional movement. Further studies on the absorption of electrolytes from the small intestine were made by Robinson, Stewart and Luckey.²⁹ Solutions of calcium chloride and of calcium lactate were circulated through Thiry-Vella fistulas in dogs. Fistulas both of the jejunum and of the lower portion of the ileum were employed. The observations indicate that water and salt pass back and forth in either direction through the intestinal wall to bring the intestinal contents into approximate osmotic equilibrium with the blood. Concentrated acid solutions of calcium chloride yielded the most calcium to the body. Acidity did not increase the absorption of calcium from lactate solutions, but the amount absorbed did increase with the concentration of the solution. Thus the particular salt of calcium involved, as well as the acidity of the solution, appeared to be of importance in determining the amount of calcium absorbed. Alkaline solutions quickly became acid. In lactate solutions this phenomenon was accompanied in part by an inflow of carbon dioxide, although some other mechanism was involved. The solution was ultimately brought to the normal reaction of that section of the intestine in which it was placed. The authors conclude that the acidosis following administration of calcium chloride is not due to the selective absorption of chloride ion from the intestine but is apparently caused by a displacement of other cations by calcium, the subsequent excretion of which produces a deficit in total blood cation.

The absorption of an amino acid mixture from the upper portion of the jejunum was studied by Zetzel and Banks³⁰ by means of the Miller-Abbott technic with the equivalent of open and closed loops. In open loops, in the upper part of the jejunum a test mixture was always diluted at the end of one-half hour to a nitrogen concentration of 2 mg. per cubic centimeter, regardless of the amount of nitrogen originally present, although this physiologic adjustment did not occur

28. Dennis, C., and Visscher, M. B.: Studies on the Rates of Absorption of Water and Salts from the Ileum of the Dog, *Am. J. Physiol.* **131**:402, 1940.

29. Robinson, C. S.; Stewart, D. E., and Luckey, F.: The Changes in Composition of Solutions of Calcium Chloride and Calcium Lactate in the Intestine, *J. Biol. Chem.* **137**:283, 1941.

30. Zetzel, L., and Banks, B. M.: Intestinal Absorption of an Amino-Acid Mixture in Normal Subjects, *Am. J. Digest. Dis.* **8**:21, 1941.

with any regularity in closed loops. The amount of nitrogen absorption in open loops varied with the amount originally introduced, although the percentage of absorption decreased as the concentration of nitrogen increased. In closed loops, however, absorption of a 15 per cent mixture showed little increase over the absorption observed when a 10 per cent mixture was given. The difference between absorption in closed loops and that in open loops would seem to have definite bearing on the problem of absorption in cases of intestinal obstruction.

The absorption of carotene from isolated intestinal loops in dogs has been studied by Irvin, Kopala and Johnston.³¹ The substance was not absorbed in any significant amounts when placed in loops in concentrated solution in cottonseed oil and in the absence of bile and pancreatic lipase. When carotene was given with bile or with lipase, significant amounts were absorbed, but much greater absorption was noted when the carotene was combined with bile and pancreatic lipase together. Pure bile salts accelerated the absorption of the test substance. In the presence of bile and lipase, the rate of absorption increased as the concentration of carotene increased. The results suggest that the choleate theory of the absorption of carotene cannot be completely abandoned, although it is not an altogether adequate explanation. The inhibiting effect of liquid petrolatum on absorption of carotene was confirmed.

Because of the frequent clinical use of novatropine, the report of Batterman and Rose³² is of some interest. These authors show that the absorption of the drug is not significantly altered if it is administered with large amounts of colloidal aluminum hydroxide.

The role of the stomach in the digestion of carbohydrate and protein has been reexamined by Beazell,³³ with some interesting results. With young normal adults as subjects, the ratio of "digested" and "undigested" protein and starch in a standard meal was determined in material recovered from the stomach at various periods after ingestion. The results, which were based on the recovery of reducing sugars and of protein reduced to a form soluble in tungstic acid, indicated that the conventional conception that the stomach plays an unimportant role in the digestion of starch and an important role in the digestion of protein is open to revision. As high as 40 per cent of the starch was found in the form of reducing sugars at the end of one hour, but only 2.5 per cent of the nitrogenous material obtainable could be classi-

31. Irvin, J. L.; Kopala, J., and Johnston, C. G.: The Absorption of Carotene from Isolated Intestinal Loops, *Am. J. Physiol.* **132**:202, 1941.

32. Batterman, R. C., and Rose, O. A.: Absorption of Novatropine in the Presence of Colloidal Aluminum Hydroxide, *Am. J. Digest. Dis.* **8**:20, 1941.

33. Beazell, J. M.: A Reëxamination of the Role of the Stomach in the Digestion of Carbohydrate and Protein, *Am. J. Physiol.* **132**:42, 1941.

fied as partially digested. Even at the end of two hours less than 10 per cent of the nitrogenous material remaining in the stomach was digested. It would appear that the importance of the stomach in the hydrolysis of starch, as a result of the action of ptyalin, has not been fully appreciated, while its importance in the hydrolysis of protein has been overemphasized.

McGee and Emery³⁴ have made a study of the factors influencing digestion in the jejunum. Determinations of the amylase and protease contents were made on normal human subjects and on patients with achlorhydria or peptic ulcer or on those who had undergone gastric resection or cholecystectomy. No significant variation in the enzyme content of the jejunal juice was observed in the various subjects investigated after the instillation of magnesium sulfate, iron and ammonium citrates, gelatin, starch, amino acids, sodium bicarbonate or hydrochloric acid. After an interval of forty-five minutes, the instillation of tenth-normal hydrochloric acid, 5 per cent solutions of amino acids, isotonic solution of sodium bicarbonate or distilled water was followed by an immediate decrease in enzyme activity of short duration, which was rapidly succeeded by a return to normal.

The motor function of the digestive tract has been studied in great detail by numerous investigators, both in animals and in human beings. The mechanical aspects of normal gastric evacuation were studied in unanesthetized dogs by Werle and his collaborators,³⁵ who simultaneously registered the intraluminal pressure of the pyloric antrum and the duodenal bulb and made fluoroscopic observations on this region. During the first period of gastric evacuation antral pressure was moderate, but the pyloric sphincter and the duodenal bulb offered little resistance to expulsion. The force of the antral wave resulted chiefly in propulsion. Because of accumulation of material in the duodenum and the contraction of the pyloric sphincter, resistance increased distally, and antral peristalsis was associated with an elevation in pressure waves. Gastric evacuation persisted under the augmented pressure head until terminated by several factors, among which was the completely contracted sphincter. Contraction of the duodenal bulb occurred, causing bulbar emptying, but regurgitation of the duodenal contents into the stomach was prevented by the tight pyloric sphincter. Van Liere and Northup,³⁶ in further experiments on variations in gastric emptying

34. McGee, L. C., and Emery, E. S., Jr.: *Factors Influencing Digestion in the Jejunum*, *Am. J. Digest. Dis.* **7**:462, 1940.

35. Werle, J. M.; Brody, D. A.; Ligon, E. W., Jr.; Read, M. R., and Quigley, J. P.: *The Mechanics of Gastric Evacuation*, *Am. J. Physiol.* **131**:606, 1941.

36. Van Liere, E. J., and Northup, D. W.: *The Emptying Time of the Normal Stomach After the Administration of a Bile Preparation*, *Am. J. Digest. Dis.* **8**: 26, 1941.

time, demonstrated in human beings an average decrease of more than 20 per cent following the oral administration of dehydrocholic acid. Card,³⁷ in studying the inhibitory effect on gastric contractions of lipids introduced into the duodenum, showed that fatty acids were far more effective than the corresponding fats in inhibiting gastric contractions. In the case of pure fats, no evidence was obtained that significant differences exist in their individual inhibiting actions.

The relation between duodenal movements and the evacuation of bile into the duodenum was studied by Murakami and Uchiyama.³⁸ By rather complicated, but apparently reasonably accurate, methods, the authors simultaneously measured the outflow of bile during fasting in human beings and recorded duodenal motility. In most instances, a flow of bile was readily demonstrated, even in the fasting state, although this phenomenon has been denied by some investigators. For the most part, the outflow of bile occurred during periods of motor activity of the duodenal wall. Infrequently no bile was observed in the duodenal drainage fluid despite continued movements of the duodenum during fasting, and the authors assume from this fact that a failure to demonstrate bile flow in the fasting state suggests an increased resistance in the region of the sphincter of the common bile duct. Experiments on animals studied by ingenious methods yielded similar results, and usually the most active flow of bile was associated with fairly vigorous duodenal motility. Only when the duodenum had entered a tetanic phase did evacuation of bile drop to its lowest point, and at this time it was noted that the resistance at the distal end of the common duct had increased to as high as 500 mm. of water. Although the constancy of these relations could not be demonstrated, there would seem to be no doubt that the normal evacuation of bile is intimately correlated with the muscular activity of the duodenal wall.

Becker and Windle³⁹ sought exhaustively for evidences of motility in the gastrointestinal tract in cat and guinea pig fetuses. Their observations are of particular interest to anatomists, especially in relation to the

37. Card, W. I.: A Comparison of the Inhibitory Action of Different Fats and Fatty Acids Introduced into the Duodenum on Gastric Contractions, *Am. J. Digest. Dis.* **8**:47, 1941.

38. Murakami, T., and Uchiyama, H.: Functions of the Extrahepatic Bile Ducts and Secretory Function of the Liver: IV. Clinical Study on the Relation Between the Duodenal Movements and the Evacuation of Bile into the Duodenum During Fasting, *Arch. Surg.* **42**:693 (April) 1941. Uchiyama, H., and Murakami, T.: Functions of the Extra Hepatic Bile Ducts and Secretory Function of the Liver: V. Experimental Study on the Relation Between the Movements of the Duodenum and the Functions of the Biliary Tract During Fasting, *ibid.* **42**:703 (April) 1941.

39. Becker, R. F., and Windle, W. F.: Origin and Extent of Gastro-Intestinal Motility in the Cat and Guinea Pig, *Am. J. Physiol.* **132**:297, 1941.

development of the myenteric and submucosal ganglions and plexuses, as well as to the timely appearance of the vagus nerve supply of the stomach and the sympatheticovagal supply from the celiac ganglions to the intestinal tract. Peristalsis became established, as was to be expected, only when circular and longitudinal muscle fibers could be demonstrated.

Duodenal movements were especially studied by Mecray,⁴⁰ with particular reference to antiperistalsis. The method employed—namely, the visualization of the duodenal wall by means of subserous injections of a colloidal suspension of thorium dioxide (thorotrast)—might conceivably throw some doubt on any interpretations based on the observations made. It would appear, however, that a sufficient number of weeks had elapsed between the injection of the thorium dioxide and the actual period of the study. Detailed descriptions of duodenal motility are given, with the suggestion that the older concepts of the “law of the intestine,” intestinal segmentation and peristaltic rush may need some revision as regards duodenal motor activity. It is of particular interest that the author failed to note any antiperistalsis in the duodenum, even during the act of vomiting.

The mechanism of vomiting following the intravenous administration of staphylococcus enterotoxin was studied under various experimental conditions by Bayliss.⁴¹ Interference with various portions of the nervous system by certain drugs or by certain surgical procedures modified the emetic effect of injected enterotoxin. The experimental results indicate that the action of the toxin on peripheral sensory structures is of greater importance in the initiation of vomiting than is the direct action of the toxin on the vomiting center. Morphine sulfate and ergotoxine ethanesulfonate inhibited or delayed the emetic action of the toxin, whereas atropine sulfate and pentobarbital sodium had little or no effect. By means of exteriorized loops of small bowel in continuity, Oppenheimer and Mann⁴² studied the role of the small intestine during emesis produced by various substances, such as apomorphine hydrochloride, antimony and potassium tartrate and carbaminoylcholine. Activity in the upper portion of the jejunum and lower part of the ileum was particularly observed. The act of vomiting was preceded by marked intestinal activity, but the authors were not able to identify antiperistalsis, although the occurrence of such a phenomenon was strongly suspected. The rate of contraction of the intestine was not altered during emesis by the drugs used, although the amplitude and

40. Mecray, P. M., Jr.: A Study of the Movements of the Duodenum with Special Reference to Antiperistalsis, *Am. J. Digest. Dis.* **8**:76, 1941.

41. Bayliss, M.: Studies on the Mechanism of Vomiting Produced by Staphylococcus Enterotoxin, *J. Exper. Med.* **72**:669, 1940.

42. Oppenheimer, M. J., and Mann, F. C.: Role of the Small Intestine During Emesis, *Am. J. Digest. Dis.* **8**:86, 1941.

character of the contractions varied widely. The reversal or flattening of the intestinal gradient known to occur during vomiting (Alvarez) appeared to be present after the administration of morphine and probably contributed both to the emesis and to the well known constipation following administration of morphine. Such a flattening of intestinal gradient would be associated with the absence of normal feeding responses and the failure of food to pass along the gastrointestinal tract.

A rather disturbing article is that by Bisgard and Nye⁴³ on the influence of the application of heat and cold on gastric and intestinal motor activity. From observations made during balloon experiments the authors conclude that gastrointestinal motor activity is inhibited by the application of heat to the abdominal wall and by iced water taken by mouth and that it is stimulated by the application of ice to the abdominal wall and by the ingestion of hot water by mouth. These findings are of interest if true. It has been frequently noted, however, that the ingestion of iced water apparently increases motility of the stomach and the small intestine and thereby enables a much more rapid fluoroscopic observation of these portions of the digestive tract. It is also a generally accepted impression that cold drinks offer much greater stimulation to intestinal activity than do warm fluids. Finally, gastroscopic observations by Brohl (1938) demonstrated increased peristaltic activity following the external application of heat to the epigastrium and the opposite effect after the application of cold. The findings of Bisgard and his collaborators are, therefore, somewhat paradoxical and warrant further study inasmuch as the therapeutic implications are of real importance.

To those interested in the mechanism underlying the production of gastrointestinal symptoms, the observations of Ingelfinger and Abbott⁴⁴ are worthy of note. These authors have augmented their previous intubation studies on the human small intestine and have obtained kymographic records of intestinal activity for a large number of well controlled subjects, both normal persons and patients suffering from disease of the digestive tract. The authors observed the caliber of the small bowel, the pattern of its large and small waves and the motility of its contents. They properly conclude that studies of such material may yield objective data that will help in an understanding of symptoms dependent on both functional and organic disturbances. It may well be that similar studies, once a really adequate knowledge of the normal

43. Bisgard, J. D., and Nye, D.: The Influence of Hot and Cold Application upon Gastric and Intestinal Motor Activity, *Surg., Gynec. & Obst.* **71**:172, 1940.

44. Ingelfinger, F. J., and Abbott, W. O.: Intubation Studies of the Human Small Intestine: XX. The Diagnostic Significance of Motor Disturbances, *Am. J. Digest. Dis.* **7**:468, 1940.

condition has been obtained, may serve as an adjunct to roentgenologic diagnosis in cases of obscure disease.

A detailed and convincing set of experiments by Hodes⁴⁵ appears to add further knowledge of the relation of the autonomic nervous system to motor activity. The author studied the effect of stimulation of the vagus and sciatic nerves in animals without available adrenal secretion. The experiments seemed to show that the vagus nerves exert a tonic motor influence on the small intestine and that central stimulation of the sciatic nerve causes intestinal inhibition and loss of tone, even after the splanchnic nerves are destroyed. This appears to be due to a decrease in the normal activity of the vagus nerve and is, therefore, an example of reciprocal innervation. With the splanchnic nerves intact and both vagus nerves sectioned, central stimulation of one vagus trunk caused at times an augmentor and at times an inhibitory reflex, a variation again suggestive of a reciprocal innervation. The decline in intestinal motility after double vagotomy seems to be explained by the unchecked reign of the tonic and reflex inhibitory activity of the splanchnic nerves. Further evidence of such a reciprocal synergism between the motor and the inhibitory system is brought out by the excellent studies of Lium,⁴⁶ who showed in animals that removal of the celiac and the superior and inferior mesenteric ganglions resulted in diarrhea and increased rectal motor activity, with the appearance of mucus and blood in the stools. Other changes, such as intussusception, gastritis, duodenitis, enteritis, hyperemia, edema of the intestine and intramucosal hemorrhages, were also noted. The chief importance of Lium's work is that it calls attention to the possible neurogenic factors influencing intestinal disturbances. It provides additional evidence that excessive parasympathetic stimulation or lack of sympathetic (inhibitory) control may lead to profound motor, and eventually to structural, changes in the digestive tract. This evidence is of obvious importance in relation to such diseases as mucous colitis, ulcerative colitis and the like.

Although not directly related to the problem of autonomic control of intestinal motility, the studies of Bentley and Smithwick⁴⁷ regarding the production of visceral pain by distention of the jejunum are of extreme interest because of their bearing on the important relation between the autonomic nervous system and the digestive tract. These authors, using the usual method of balloon distention of the small bowel.

45. Hodes, R.: Reciprocal Innervation in the Small Intestine, *Am. J. Physiol.* **130**:642, 1940.

46. Lium, R.: Peptic Ulcer and Diarrhea Following the Removal of the Pre-vertebral Ganglia in Dogs: The Antispasmodic Effects of Magnesium Sulfate, Pentobarbital and Atropine Sulfate, *Surgery* **9**:538, 1941.

47. Bentley, F. H., and Smithwick, R.: Visceral Pain Produced by Balloon Distention of the Jejunum, *Lancet* **2**:389, 1940.

were able to produce abdominal pain or distress similar to that observed by numerous investigators. Of particular interest is their comparison of sensations so produced in normal subjects with the results of similar procedures carried out on patients who had undergone unilateral and bilateral splanchnicectomy and lumbar sympathectomy. After unilateral splanchnicectomy and lumbar sympathectomy, pain produced by distention of the upper jejunum was felt only on the side of the abdomen which had not been operated on. After bilateral operation no pain was experienced. There are few more striking examples of the mechanism of visceral sensation. The authors argue that visceral sensation is not a distinct type of sensation, with a special and separate physiologic basis, and feel that the difference between somatic and visceral sensation is one of degree.

The association of serious interference with the normal motor activity of the digestive tract and peritonitis is well known. Studies by Douglas and Mann⁴⁸ are of interest in this connection. These authors observed the effects of intraperitoneal irritation on extraperitoneal loops of the cecum or ileum in animals. The production of peritoneal irritation was constantly associated with prolonged arrest of movements in the extraperitoneal loop, even after degenerative section of both vagus nerves and of one splanchnic nerve and bilateral adrenalectomy. The arrest was in the nature of reflex inhibition, and the authors concluded that prolonged intestinal inhibition resulting reflexly from irritation of the peritoneum is mediated by the splanchnic nerves. They feel that there is a sound physiologic basis for the neurologic concept of paralytic ileus.

Visualization of the motor activity of the colon by a colonmetrogram was obtained by White, Verlot and Ehrentheil⁴⁹ in a study of the neurogenic disturbances of the colon. This method has only recently been used and is entirely analogous to similar methods of studying the urinary bladder. The peristaltic contractions of the colon appear to be a form of stretch reflex, the afferent and efferent arcs of this spinal reflex running over the parasympathetic sacral rami, over the second, third and fourth sacral roots in the cauda equina and over the corresponding segments in the lower end of the spinal cord. The normal patient appears to become aware of a sensation in the colon or bladder at a pressure between 20 and 30 cm. of water, and at a pressure of 40 to 50 cm. there is a real urge to defecate or urinate. Lesions in the brain, spinal cord and sacral nerves produced characteristic disturbances in the physiologic mechanism of evacuation common both to colon and to

48. Douglas, D. M., and Mann, F. C.: The Effect of Peritoneal Irritation on the Activity of the Intestine, *Brit. M. J.* **1**:227, 1941.

49. White, J. C.; Verlot, M. G., and Ehrentheil, O.: Neurogenic Disturbances of the Colon and Their Investigation by the Colonmetrogram, *Ann. Surg.* **112**: 1042, 1940.

bladder and analogous to alterations in the knee jerk and other tendon jerks which are dependent on the stretch reflex of skeletal muscle. These studies of White and his collaborators present important information regarding colonic disturbances in relation to lesions of the motor fibers in the brain or descending spinal tracts, which produce hyper-tonic responses to filling, or to lesions in the sacral segments of the cord, cauda equina or pelvic plexuses, which tend to be productive of an atonic bowel. Such findings again stress the importance of the autonomic nervous system in its relation to motor activity of the intestine, as well as to the direct application of such a consideration to various neuro-surgical conditions.

The motility of the human colon was carefully studied by Adler, Atkinson and Ivy⁵⁰ in 4 healthy subjects. Seventy experimental periods formed the basis of the observations, and all periods, whether in the morning or the afternoon, were of at least two and a half hours' duration. Single and tandem balloons were used. According to these observers, the portion of the human colon studied manifested qualitatively the same types of motility as did the colon in dogs. Various types of contraction were noted, propulsive and otherwise. Adjacent segments of the colon during the greater part of any period of study did not simultaneously manifest integrated motility. At times, the distal segment did not respond by "accepting" the propagated wave from above, and a mild cramplike sensation occasionally was felt. The authors suggest that this phenomenon in an exaggerated form may provide an explanation for the "unstable," "irritable" or "ataxic" colon which produces symptoms in the absence of definite roentgenologic evidence of localized spasticity of a segment. Functionally, such a colon manifests dyskinesia. Although the quantity and quality of motility were subject to variation, when numerous control records were made the average did show that the ratio between total motility and propulsive motility was constant in different subjects. In view of the controversy regarding antiperistalsis, it is of interest to note that the authors observed rare instances of antiperistalsis of the proximal portion of the descending colon. On this basis, they asserted, but could not prove, that the presence of material in the colon conditions the response to the so-called "feeding," or "gastrocolic," reflex. The motility of the colon was depressed by sleep and was augmented on awakening.

Numerous further studies on the effects of drugs on gastrointestinal motility continue to appear. A complete investigation, part of which

50. Adler, H. F.; Atkinson, A. J., and Ivy, A. C.: A Study of the Motility of the Human Colon: An Explanation of Dysynergia of the Colon, or of the "Unstable Colon," *Am. J. Digest. Dis.* 8:197, 1941.

was rather thoroughly reviewed a year ago, is that of Myers,⁵¹ on the effects of morphine, diacetylmorphine and some related alkaloids on the alimentary tract in cats. His most recent experiments are directed particularly at the probable mechanism of the constipating action of morphine. Because of the previous review, Myers' results will not be discussed in detail. Certain points of clinical importance may be mentioned briefly, however, and attention is drawn to the excellent tabulation of the observed effects of morphine hydrochloride, diacetylmorphine (heroin), codeine phosphate, dilaudid hydrochloride, dihydrocodeinone hydrochloride (dicodid) and dihydrooxycodone hydrochloride (eukodal). Morphine causes a marked delay in the passage of food from the stomach to the duodenum and further delays its normal passage along the small intestine because of a marked increase in tone, which is similar to, but not so great as, that due to lead salts. As in the case of the pyloric sphincter, the ileocolic sphincter remained closed for a longer period than normal and thus delayed the passage of food residue into the cecum. Delay in the colon was least marked and possibly was compensated for by a secondary increase in colonic motility. With larger doses, colonic peristaltic movements may be even suppressed, and because of the delay in the small intestine, food residue would be more plastic and therefore more difficult to propel than fluid contents. A second phase of increased tone in the colon contributed to further delay, and, in addition, the relaxation of the rectal musculature, which occurred at the end of five or six hours, permitted the rectum to become loaded to a marked degree. A further complicating factor in this series of events undoubtedly is the distinct diminution, due to the morphine, of the reaction to external and internal afferent impulses. Diacetylmorphine (heroin) caused more marked delay in gastric emptying because of pyloric spasm, but in the small and large bowels the action was less prolonged. This drug apparently arrests the progress of alimentary contents at two points, the pyloric and the ileocolic sphincter, whereas morphine causes a general slowing along the entire intestinal tract, as well as at these two sphincters. Codeine, dihydrocodeinone hydrochloride (dicodid) and small doses of dihydrooxycodone hydrochloride (eukodal) caused little deviation from the normal motility of the alimentary tract. Dilaudid hydrochloride seemed to have an effect similar to that of morphine, but the delay caused by it was much shorter than that due to morphine or to diacetylmorphine (heroin). It actually appeared to cause motor activity in the large intestine, which speeded up the passage of contents into the rectum. In the case of dihydrooxycodone

51. Myers, G. N.: The Effects of Morphine, Diacetylmorphine, and Some Related Alkaloids upon the Alimentary Tract: V. A Discussion of the Probable Mechanism of the Constipating Action of Morphine, *J. Hyg.* **40**:583, 1940.

(eukodal), larger doses apparently may postpone the defecation reflex beyond the six-hour stage, and under such circumstances constipation may follow.

Forster⁵² studied to advantage the motor activity of the small bowel in a patient with intestinal polyps involving the lower third of the ileum. It appeared that the motor activity of exteriorized ileum in this patient was either propulsive or nonpropulsive in nature, in other words "peristaltic" or "mixing." Morphine sulfate, in doses of $\frac{1}{8}$ grain (8.1 mg.), completely suppressed peristaltic waves, as other investigators have observed, but increased the frequency of the mixing waves, although a subsequent dose decreased the frequency of the latter and increased the tone of both muscle coats. A diminution of both forms of motor activity resulted from the injection of $\frac{1}{150}$ grain (0.41 mg.) of atropine sulfate; a second dose produced complete suppression of the peristaltic wave and almost complete absence of the mixing wave, with an occasional loss in tone of the longitudinal muscle coat.

Templeton and Adler⁵³ have also studied the effect of morphine on transportation in the colon. In rather complicated experiments on dogs, the relation of transportation force to motility in the colon was observed and subsequent modifications caused by morphine were noted. After the administration of moderate doses of morphine sulfate, the rate of transportation of a bolus in the colon was immediately augmented, then retarded. The force exerted by the colon to transport a bolus was measured by an isometric technic which revealed a close correlation between that force and the character, rather than the quantity, of activity. The dual effect of morphine is described as first, augmentation and, second, retardation of the normal "efficiency gradient." The phase of retardation in the normal "efficiency gradient," in which activity in the lower segments more nearly approaches that of the proximal segments, may account, the authors believe, for constipation following administration of morphine.

Adler and Ivy⁵⁴ studied the antagonistic action between morphine and atropine. The effect of these two alkaloids on the motility of the colon was followed in dogs trained to lie quietly, and it was noted that the injection of morphine caused a temporary increase in tone and in propulsive and nonpropulsive motility of the colon. Fifty per cent of the propulsion of great magnitude occurred in the first twenty minutes

52. Forster, A. C.: The Production of Hyper- and Hypomotility of the Musculature of the Small Bowel in the Human, *Ann. Surg.* **112**:370, 1940.

53. Templeton, R. D., and Adler, H. F.: The Relation of Transportation Force to Motility in the Colon of the Dog, *Am. J. Physiol.* **130**:69, 1940; The Influence of Morphine on Transportation in the Colon of the Dog, *ibid.* **131**:428, 1940.

54. Adler, H. F., and Ivy, A. C.: Morphine-Atropine Antagonism on Colon Motility in the Dog, *J. Pharmacol. & Exper. Therap.* **70**:454, 1940

after the injection of the drug. Previous injection of atropine completely antagonized the propulsive activity produced by morphine, but had slight effect, if any, on the tone and on nonpropulsive activity. When relatively smaller doses of morphine were given, the atropine completely antagonized both types of motor activity. Atropine alone depressed the spontaneous motility of the colon for a variable length of time (one to several hours), the distal portion of colon being depressed for a longer time than the proximal portion.

Further studies on the antispasmodics trasentin (diethylaminoethyl ester of diphenyl acetic acid) and trasentin-6H (diethylaminoethyl ester of phenylcyclohexyl acetic acid) were made by Graham and Lazarus.⁵⁵ Trasentin, which inhibits the normal tone and movements of isolated rabbit's intestine and relaxes spasm caused by barium chloride and physostigmine salicylate, was only one-third as powerful as spasmolytic as was trasentin-6H. The latter drug was between five and ten times as effective in inhibiting the tone and movements of the small bowel in intact rabbits anesthetized with ether and in cats on which section of the spinal cord had been done and in the cats caused relaxation of the stomach. When compared with atropine, trasentin-6H in doses which inhibited the tone of the gastrointestinal tract had little effect on salivation produced by pilocarpine, on the rate or action of the heart, on the size of the pupil, on respiration or on the parasympathetic nerve supply to the cardiovascular system. The drug is about 25 per cent more toxic than atropine but has a proportionately greater spasmolytic action. In antagonizing the action of such muscular stimulants as barium chloride, it is almost as potent as papaverine, inasmuch as it is relatively free from side effects. The author properly concludes that trasentin-6H seems worthy of clinical trial. The spasmolytic action of atropine-methylnitrate (eumydrine) was also studied by Graham and Lazarus⁵⁶ and was compared with that of atropine sulfate. Both drugs antagonized the neurogenic action of physostigmine salicylate on the intestinal tract and appeared to be of comparable potency. Although the effects of the two drugs were about equal in reducing the tone and segmental movements of the intestine, the toxicity of atropine methylnitrate (eumydrine) was approximately three times as great as that of atropine. In studies on anesthetized and unanesthetized human beings, Martin and Batterman⁵⁷ confirmed previous observations on the spasmolytic action

55. Graham, J. D. P., and Lazarus, S.: Action of Synthetic Antispasmodics "Trasentin" and "Trasentin-6H," *J. Pharmacol. & Exper. Therap.* **69**:331, 1940.

56. Graham, J. D. P., and Lazarus, S.: The Action of Methyl-Atropine Nitrate (Eumydrin), *J. Pharmacol. & Exper. Therap.* **70**:165, 1940.

57. Martin, S. J., and Batterman, R. C.: The Control of Gastro-Intestinal Tone and Motility with Novatropine, *Anesthesiology* **1**:300, 1940.

of novatropine. Doses ranging from 2.5 to 7.5 mg. eliminated or markedly reduced the tone and motility of the gastrointestinal tract. Use of the drug is recommended by these authors as of advantage in surgical procedures on the abdomen.

The effect of the injection of bacterial vaccines on colonic activity was the subject of an investigation by Adler and his colleagues.⁵⁸ Tandem balloons were placed in the colons of the experimental animals, and colonic motility was observed after the intravenous injection of vaccines prepared from *Escherichia coli* communior, *Spirillum rubrum* and *Staphylococcus aureus*. Injections of *E. coli* communior produced an initial slight depression in motility, followed by a period of increased motor activity and subsequently by profound depression of all motor activity, which persisted for several hours before a return to normal. Numerous side effects were noted, including vomiting, defecation and spontaneous urination. The injection of *S. rubrum* and *Staph. aureus* produced similar effects. It is unfortunate that further studies were not carried out on organisms not usually found in the gastrointestinal tract and on the effects of nonbacterial protein preparations.

Oppenheimer and Mann,⁵⁹ in animals with exteriorized loops of small intestine in continuity, observed the effects of magnesium sulfate, cascara sagrada, mild mercurous chloride, castor oil, arecaline hydrobromide and carbaminoylcholine. None of the agents studied changed the rate of contraction of the small intestine, and the authors feel that this result, as well as observations in earlier studies, justifies the impression that the rate of contraction of the intact small intestine in continuity, with nerve and blood supply intact, is not easily altered. They suggest that the giving of food soon after the use of magnesium sulfate should be avoided, since the feeding reaction ("gastrocolic reflex") is depressed and food might not be moved properly along the gastrointestinal tract. Cascara sagrada disturbed motility and feeding response least of the drugs studied. Its effect was largely on tone, as noted by other investigators, and its action was mainly on the colon. The work of previous investigators on the action of mild mercurous chloride was confirmed. It acts largely on the upper part of the small intestine, the amplitude of contractions being more marked at the higher levels, particularly in the upper part of the jejunum; the lower portion of the ileum was the least affected. Castor oil, although it markedly increased peristalsis, did not

58. Adler, H. F.; Templeton, R. D.; Ferguson, R. L., and Galapeaux, E. A.: The Motor Reaction of the Dog's Colon to Intravenous Injections of *E. Coli* Communior, *Spirillum Rubrum*, and *Staphylococcus Aureus*, *Am. J. M. Sc.* **200**: 514, 1940.

59. Oppenheimer, M. J., and Mann, F. C.: Influence of Cathartics on the Activity of the Small Intestine, *Am. J. Digest. Dis.* **8**:90, 1941.

alter the rate. The two drugs arecaline and carbaminoylcholine, which are used extensively in veterinary medicine and the action of which is due to stimulation of the nerves of the gastrointestinal tract, increased motor activity markedly but, like the other drugs, failed to alter the intestinal rate.

An experimental study of the effect of the pituitary gland on the gastrointestinal tract was carried out by Morrison and Feldman.⁶⁰ Hypophysectomy in normal dogs did not affect gastrointestinal motility or gastric secretion. The administration of extract of the anterior lobe of the pituitary gland had no effect on motility in normal or in hypophysectomized dogs.

An interesting study on a common source of gastrointestinal symptoms is that of Wallace,⁶¹ who reports on the gross effect on the small intestine of protracted deep pelvic irradiation, with particular reference to "roentgen sickness." In a series of patients with cancer of the cervix, the small intestine was examined before and after a series of high voltage roentgen irradiations of the pelvis. Doses of as high as 2,200 from each of two anterior, two posterior and two lateral portals were used. No effects were noted in the duodenum or in the jejunum. The ileum showed changes which included segmentation of the barium sulfate stream, flattening of the mucosal pattern, diminished motility and narrowing of the lumen. The ileal changes appeared to be independent of more than 20 per cent variation in the total dose or of other variations in the irradiation technic. In view of the widespread administration of vitamin concentrates, particularly vitamin B₁ (thiamine hydrochloride) and nicotinic acid, as prophylactic and therapeutic measures in roentgen sickness, it is of interest to note that Wallace believes that there is no true roentgenologic evidence that the syndrome of roentgen sickness bears any relation to the deficiency states.

An unusual paper is that of Beazell and Ivy,⁶² who attempted to measure the quantity of colonic flatus passed in twenty-four hours by five "normal" ambulatory subjects. The gas was collected in a thick-walled rubber balloon by means of a colon tube. The volume varied between 380 and 655 cc. There was no essential difference between the quantity of gas egested during the day and that egested during the night. The composition of the gas was subject to relatively wide variation.

60. Morrison, S., and Feldman, M.: An Experimental Study of the Effect of the Pituitary on the Motility of the Gastrointestinal Tract, *Am. J. Digest. Dis.* 7:451, 1940.

61. Wallace, W. S.: The Intestine in Radiation Sickness: I. The Gross Effect on the Small Intestine of Protracted Deep Pelvic Irradiation, *J. A. M. A.* 116: 583 (Feb. 15) 1941.

62. Beazell, J. M., and Ivy, A. C.: The Quantity of Colonic Flatus Excreted by the "Normal" Individual, *Am. J. Digest. Dis.* 8:128, 1941.

Such a study, while not complete in itself, may well form the basis for a set of control observations to be compared with subsequent studies on the results of alterations in diet and "intestinal fermentation."

Another phase of the anatomophysiologic aspect of gastroenterology is that involving the circulation. Wilmer⁶³ has made a careful anatomic study of the blood supply of the first portion of the duodenum, which is described in great detail. The complexity of the gastroduodenal plexus suggests to the author that it is unlikely that vessel ligation will suffice to control bleeding in massive hemorrhage from an ulcer on the posterior wall of the duodenum. Such a statement, based on adequate anatomic studies, is of obvious importance in relation to the surgical treatment of bleeding peptic ulcer.

Kuntz and Haselwood⁶⁴ report on the circulatory reactions in the gastrointestinal tract elicited by localized cutaneous stimulation. The investigation was undertaken to determine whether appreciable circulatory changes in the visceral organs could be brought about by means of localized cutaneous stimulation. Experiments were carried out on decerebrated cats in order to avoid the effects of anesthesia. Applications of heat and cold and vacuum cups were employed as stimulating agents on the dorsal and lateral surfaces of the trunk. The changes in the blood vessels of the stomach and intestine were recorded photographically and plethysmographically. In some instances the splanchnic nerves were sectioned and the sympathetic lumbar trunks were extirpated. Changes in the caliber of the gastrointestinal vessels corresponded to those produced in the cutaneous vessels in the area stimulated. Moderate localized warming of the skin (45 to 50 C. [113 to 122 F.]) and the application of vacuum cups produced dilatation in the cutaneous areas stimulated and in the corresponding segments of the gastrointestinal tract. Localized warming of the skin to (52 C. [125.6 F.]) or more caused initial vasoconstriction in the gastrointestinal tract. Moderate localized cooling of the skin resulted in vasoconstriction in the cutaneous areas stimulated and in the corresponding segments of the intestine. The changes in the caliber of the blood vessels of the gastrointestinal tract were more marked in the smaller ones than in the larger. The vascular changes were sufficiently marked to warrant the conclusion that the volume of blood flowing through the affected segments of the gastrointestinal tract is markedly decreased by localized cooling and markedly increased by localized warming of the skin. The authors concluded that

63. Wilmer, H. A.: The Blood Supply of the First Part of the Duodenum, *Surgery* 9:679, 1941.

64. Kuntz, A., and Haselwood, L. A.: Circulatory Reactions in the Gastrointestinal Tract Elicited by Localized Cutaneous Stimulation, *Am. Heart J.* 20: 743, 1940.

these phenomena can be explained as reflex reactions mediated through segmental and intersegmental cutaneovisceral reflex arcs. Stimulation of the receptors involved in these reflex reactions seems probably associated with a change in the tonic state of the cutaneous blood vessels in the area in question.

Klemperer, Penner and Bernheim⁶⁵ have continued their work on the gastrointestinal manifestations of shock. In order to test the validity of the vasospastic theory of the origin of intestinal lesions occurring in shock, the authors performed experiments on various animals and attempted to reproduce the type of vasospasm known to occur in shock. They discovered that the pathogenesis of lesions observed in the cat was identical with that observed in the dog, while in the rat and guinea pig it was similar to that in man. Under conditions of shock caused by the intraperitoneal administration of epinephrine, gastrointestinal lesions were found which reproduced all of the various stages to be observed in human subjects at autopsy. In man, the sequence of events leading to mucosal ulceration seems to involve a short circuiting of blood flow through the arteriovenous anastomoses associated with vasoconstriction in the other terminal branches of the submucosal arterioles. This leads to a deviation of the blood flow through the villi, since arteriovenous anastomoses are located in these structures. The simultaneous vasoconstriction of the other terminal branches of the submucosal arterioles leads to submucosal anoxemia, which, if severe and persistent, may result in the tissue changes found in human beings during shock.

The effects of distention on blood flow through the intestine were examined in dogs by Lawson and Chumley.⁶⁶ The blood flow through loops of small intestine was only momentarily interrupted by inflation of the loops under pressures below 30 mm. of mercury. Inflation at higher pressures below mean mesenteric arterial pressure caused an initial marked reduction in flow, from which there was a partial recovery within a few seconds. Simple transverse stretching of a strip of intestine opened along its antimesenteric border sometimes caused a simple increase in flow. If enlargement of the loop was prevented by counter-pressure or if the loop was treated with cocaine or procaine, any rise in intraluminal pressure caused a reduction in flow which persisted without any tendency toward recovery, or with reduced recovery, throughout the inflation. In untreated loops, hyperemia followed deflation, but the hyperemia was sometimes interrupted by a transient period of reduced flow, apparently due to deflation hypermotility. No phase of response to

65. Klemperer, P.; Penner, A., and Bernheim, A. I.: The Gastro-Intestinal Manifestations of Shock, *Am. J. Digest. Dis.* **7**:410, 1940.

66. Lawson, H., and Chumley, J.: The Effect of Distention on Blood Flow Through the Intestine, *Am. J. Physiol.* **131**:368, 1940.

inflation was significantly modified by perivascular mesenteric denervation. The authors suggest that stretching the walls of the intestine during inflation sets up vasodilatation through intrinsic nerve mechanisms, which results in local circulatory compensation for the added resistance to flow.

CLINICAL ASPECTS

Esophagus.—Little has been added to knowledge of esophageal disturbances, and a review by Bird in 1939 can still be utilized as the most important recent reference for diseases of this portion of the digestive tract. A brief review by Vinson⁶⁷ covers many of the important articles in the literature that have appeared during the past year. Since, for the most part, esophageal symptoms are those associated with motor disturbances, it is important to stress the various ways in which abnormalities in motility may arise and form the basis of symptoms. Faulkner⁶⁸ presents an important review regarding the initiation of many disturbances in motility. His detailed outline of the objective esophageal changes due to psychic factors is based on an esophagoscopy study, with a report of 13 cases in which the esophagus was visualized directly. Symptoms referable to the esophagus were present in all cases. Emotional upsets of an unpleasant nature, causing anxiety, anger or a similar state, resulted in definite spasm of the lower end of the esophagus, with narrowing or closure of the lumen. On the other hand, complete relaxation practically always occurred when any of these emotional states was relieved. The esophageal reactions and the associated alterations in spasm were directly related to the patient's personal interest in any given problem, whereas one in which the patient had no vital interest was incapable of eliciting an esophageal reflex. The author also observed the important relation between this type of motor disturbance and organic changes, such as esophageal stricture, cardiospasm and pressure diverticulum. This point of view is not novel, but it is absolutely essential for the proper understanding and treatment of the mechanism underlying symptoms.

Obviously, organic narrowing of the esophagus is per se an important cause of symptoms. Congenital atresia of the esophagus has been thoroughly reviewed by Lanman,⁶⁹ who presents a gloomy picture of surgical attempts to cure this rather uncommon condition. Lanman points

67. Vinson, P. P.: A Review of English Literature on Diseases of the Esophagus for 1940, *Am. J. Digest. Dis.* 8:202, 1941.

68. Faulkner, W. B., Jr.: Objective Esophageal Changes Due to Psychic Factors: Esophagoscopy Study with Report of Thirteen Cases, *Am. J. M. Sc.* 200:796, 1940.

69. Lanman, T. H.: Congenital Atresia of the Esophagus: A Study of Thirty-Two Cases, *Arch. Surg.* 41:1060 (Nov.) 1940.

out, however, that surgical measures are becoming more and more standardized and that a radical cure may properly be expected as more experience is gained in the diagnosis and treatment.

The importance of prompt recognition and treatment of foreign bodies in the esophagus is obvious. In a report of several interesting cases Vistreich⁷⁰ emphasizes the condition and the complications that may arise from delayed or improper treatment.

Polypoid tumor is uncommon, but the possibility of such a benign lesion is stressed by Mahoney,⁷¹ who logically recommends that all such lesions should be considered malignant until proved otherwise by adequate biopsy. Leiomyosarcoma is extremely rare. One instance is reported by French and Garland.⁷²

Carcinoma, of course, offers the greatest challenge to surgeons at present. It is carefully considered by Garlock,⁷³ who reports his experience of the last four and a half years, during which he has operated on 20 patients, in 14 of whom the lesion was operable. There is little doubt that the skilled surgeon approaches this serious problem with gradually increasing chances of some success from proper operative procedures. That a malignant condition may develop in the presence of benign stricture of the esophagus is stressed by Benedict,⁷⁴ who reports 2 cases of such a complication. Here, again, emphasis is laid on the fact that careful esophagoscopy examination is essential, with the removal of adequate specimens for biopsy when indicated, in order to establish a diagnosis and to outline proper treatment.

The occurrence of acute ulcerative esophagitis due to numerous causes is reviewed by Bloch.⁷⁵ This condition is extremely uncommon and in most instances is difficult to diagnose. It is also difficult to assign an adequate cause in the absence of localized primary disease. Vomiting, nasal intubation, shock, arteriosclerosis, diseases of the brain, severe general and local infections and pneumonia have all been implicated, but frequently without adequate proof. It is important to recognize that such a condition may occur, although the diagnosis is difficult.

The importance of tuberculosis in causing a localized necrotizing process secondary to involvement of the mediastinal lymph nodes, bronchi

70. Vistreich, F.: Two Cases of Esophageal Foreign Body with Complications, *Laryngoscope* **50**:1178, 1940.

71. Mahoney, J. J.: Polypoid Tumors of the Esophagus, *Laryngoscope* **50**: 1086, 1940.

72. French, L. R., and Garland, L. H.: Leiomyosarcoma of the Esophagus, *Am. J. Roentgenol.* **45**:27, 1941.

73. Garlock, J. H.: Problem of Cancer of Esophagus, *J. Mt. Sinai Hosp.* **7**:349, 1941.

74. Benedict, E. B.: Carcinoma of the Esophagus Developing in Benign Stricture, *New England J. Med.* **224**:408, 1941.

75. Bloch, L.: Acute Ulcerative Esophagitis, *Am. J. Digest. Dis.* **7**:407, 1940.

or lungs is fairly well recognized by phthisiologists. Primary tuberculous infection of the esophageal wall is rare, and the report by Clerf⁷⁶ is therefore of clinical interest. It is of particular interest that no other demonstrable tuberculous lesions existed in the case he describes and that local drainage of the infected area resulted in an apparent cure.

Syphilis is known at times to involve the esophagus. The number of cases is not large, but it is important to recognize that such a lesion may exist. The report of Kampmeier and Jones⁷⁷ on esophageal obstruction due to gumma of the esophagus or the diaphragm is worthy of note.

In recent years the importance of the roentgenologic demonstration of esophageal varices has been recognized, in this country largely as a result of the work of Schatzki. His review⁷⁸ of this particular roentgenologic method is of real importance and represents a definite contribution to the diagnosis and prognosis of hepatic or splenic disease. The report is based on observations in 116 cases in which varices were demonstrated. It is well illustrated, with important comments on technic and sources of error, including tortuous normal folds, small hiatus hernias, "curling" and carcinoma. It should be pointed out that not infrequently the demonstration of esophageal varices not only confirms the diagnosis of serious intrahepatic disease but constitutes important evidence of prognostic value.

The treatment of esophageal varices has long been a challenge to the surgeon. Various maneuvers, such as omentopexy, splenectomy and ligation of the coronary veins, have been attempted, with results that are far from satisfactory. The experience of Moersch and his collaborators,⁷⁹ reported a year ago, has been further extended and should be watched with a great deal of interest. Five cases have been added to the original one described, and the results are sufficiently encouraging to warrant further trial of the treatment of esophageal varices by injection. It is to be seriously hoped that this brilliant type of technical approach may receive the attention it deserves by men carefully trained in esophagoscopy. As the authors point out, the method is still on trial and should be reserved for cases in which careful studies and follow-up observations have been made.

76. Clerf, L. H.: Tuberculous Periesophageal Abscess Producing Stenosis: Report of One Case, *Ann. Otol. Rhin. & Laryng.* **49**:793, 1940.

77. Kampmeier, R. H., and Jones, E.: Esophageal Obstruction Due to Gummata of Esophagus and Diaphragm, *Am. J. M. Sc.* **201**:539, 1941.

78. Schatzki, R.: Roentgen Demonstration of Esophageal Varices, *Arch. Surg.* **41**:1084 (Nov.) 1940.

79. Walters, W.; Moersch, H. J., and McKinnon, D. A.: Bleeding Esophageal Varices, *Arch. Surg.* **41**:1101 (Nov.) 1940.

The occasional appearance of peptic ulceration in the esophagus in adults is well recognized. A detailed pathologic study of aberrant gastric mucosa in the esophagus in infants and in children is of interest in this connection. Rector and Connerley⁸⁰ present a study of 1,000 infants and children, 118 of whom were found at autopsy to have some type of aberrant gastric mucosa in the esophagus. In over 90 per cent such mucosa was limited to the upper two thirds of the esophagus; in only 8 per cent did it occur in the lower third, which is the usual site of peptic ulcer in the adult. Inflammation, with or without ulceration, was present in many of the specimens examined.

An unusual complication of cardiospasm is that of a youth aged 19 years reported by Ball and Crump.⁸¹ Evidently, as a result of a long period of cardiospasm, which the patient had tried to overcome by swallowing large amounts of air and pushing against his diaphragm in order to get fluid into his stomach, the esophagus had become markedly hypertrophied. Subsequently, the diaphragmatic opening had become greatly enlarged, with the result that the lower third of the esophagus had prolapsed into the abdominal cavity, leaving the cardia of the stomach at the upper and left-hand side of the resulting blind pouch of the esophagus. The symptoms were successfully alleviated by a side to side anastomosis.

An excellent summary on the congenital short esophagus, with thoracic stomach and esophageal hiatus hernia, is presented by Polley.⁸² In the main, the most important symptoms of the condition are presented, although too little attention is paid to the variation in symptoms that may occasionally simulate disease of other organs in the mediastinum. The author points out one interesting clinical fact not previously noted in the literature, namely, the high incidence of a coexisting diverticulum of the large bowel. Such an anomaly was present in nearly one half of the entire series, although frequently it was without associated symptoms. This and the occasional appearance of a diverticulum in the duodenum add further evidence to a suggestion that has often been made, that hiatus hernia is frequently the result of a congenital malformation. Such a probability is further stressed by Ladd and Gross,⁸³ who reviewed 25 cases of congenital diaphragmatic hernia encountered in infants. Of the 16 infants in this group who were operated on, 9

80. Rector, L. E., and Connerley, M. L.: Aberrant Mucosa in the Esophagus in Infants and in Children, *Arch. Path.* **31**:285 (March) 1941.

81. Ball, R. P., and Crump, A. C.: Mega-Esophagus (Cardiospasm), *Radiology* **36**:575, 1941.

82. Polley, H. F.: Congenital Short Esophagus with Thoracic Stomach and Esophageal Hiatus Hernias, *J. A. M. A.* **116**:821 (March 1) 1941.

83. Ladd, W. E., and Gross, R. E.: Congenital Diaphragmatic Hernia, *New England J. Med.* **223**:917, 1940.

recovered; 7 of them were less than 1 year old. The authors believe that the condition can best be diagnosed by the use of a contrast medium, preferably not a barium compound, and are convinced that early operation, which in 2 cases was performed in the first forty-eight hours of life, is advantageous. Obviously, cases of such a condition in infancy are rare but are of great importance, and that this type of defect is of minor degree is undoubtedly a factor contributing to the frequency of congenital diaphragmatic defect in adults.

An unusual complication of this condition is noted by Diddle and Tidrick,⁸⁴ who report that a patient died during the first stage of her fourth labor of strangulation of the viscera in a left-sided diaphragmatic hernia. It is of interest that the patient had had three previous uneventful deliveries, two of which had occurred after the diaphragmatic hernia had been discovered. The rarity of such a complication is unquestionably due to the fact that in most instances the symptoms of diaphragmatic hernia do not become evident until the later decades of life. The differentiation between diaphragmatic hernia (traumatic) and eventration after severe crushing injury of the chest is discussed by Faulkner,⁸⁵ who points out the diagnostic value of pneumothorax, or of pneumoperitoneum in case the other procedure is not possible because of adhesions.

Numerous descriptions of the Plummer-Vinson syndrome can be found in the literature. The article by Kernan⁸⁶ provides little that is new, except a possible explanation for the occasional association of esophageal webs with this syndrome. Although the author is unable to prove his suggested hypothesis, it is of extreme interest to speculate as to the possibility that the atrophy of the esophageal mucous membrane which undoubtedly occurs in this form of deficiency disease may be responsible for subsequent erosion and inflammatory necrosis, which in turn may lead to fibrosis and web formation.

Stomach.—The widespread use of the gastroscope has undoubtedly familiarized physicians with its important diagnostic value. There is still a reasonable hesitation among many clinicians to accept without question positive gastroscopic evidence as an explanation for symptoms. Such a hesitation is still warranted, although undoubtedly this newer method of diagnosis has contributed greatly to the understanding of various rather vague symptoms and to the knowledge of what actually goes on in many gastric disturbances, and comment on the limitations of

84. Diddle, A. W., and Tidrick, R. T.: Diaphragmatic Hernia Associated with Pregnancy, *Am. J. Obst. & Gynec.* **41**:317, 1941.

85. Faulkner, W. B. Jr.: Diaphragmatic Hernia and Eventration, *Am. J. Roentgenol.* **45**:72, 1941.

86. Kernan, J. D.: Plummer-Vinson Syndrome: Report of Two Cases, *Arch. Otolaryng.* **32**:662 (Oct.) 1940.

the method is timely. Jankelson and McClure⁸⁷ call attention to the obvious but still overlooked fact that visible changes in the gastric mucosa are not necessarily the basis for symptoms and stress the extreme importance of obtaining a wide experience before attempting to correlate clinical and gastroscopic findings. A possible source of error, which is familiar to the older, more experienced gastroscopists, is still worthy of note, namely, the effect of inflation of the stomach on the gastroscopic picture. Ruffin, Brown and Clark⁸⁸ draw particular attention to this, and the warnings implied in their paper should be taken seriously. The illustrations in the article are self explanatory and demonstrate convincingly the way in which the appearance of the stomach can be modified by improper inflation. The indications for gastroscopy are by now fairly well recognized, but for those interested in reviewing the subject, and particularly for those clinicians who are in doubt as to the real usefulness of the method as a diagnostic procedure, the paper by Benedict⁸⁹ is clear and convincing. I⁹⁰ have attempted to add a protesting note, also, against the too enthusiastic use of the gastroscope and to stress the difficulties still inherent in the various classifications of gastritis. Much work remains to be done before the gastroscopic picture and the associated histologic findings are correlated, and it seems pertinent to emphasize particularly the impropriety of terming all atrophic lesions of the stomach "atrophic gastritis" in view of the fact that a large proportion of them are merely reflections of an underlying deficiency condition, similar to the changes in the mouth associated with avitaminosis, iron deficiency and the like.

The need for continued caution in attempting to explain symptoms on the basis of gastroscopic findings is evident in an article by Flexner and Fleishman,⁹¹ who obtain, on the basis of over 250 examinations, the same percentage of various types of gastritis as was noted by Schindler. This is in such sharp contrast to some other reports by experienced gastroscopists, such as the paper by Ruffin, Brown and Clark, that it at least exemplifies the discrepancy between the point of view of the conservative but experienced gastroscopists and that of those who are more prone to explain any symptoms on the basis of minor changes in

87. Jankelson, I. R., and McClure, C. W.: Limitations of Gastroscopy, New England J. Med. **224**:64, 1941.

88. Ruffin, J. M.; Brown, I. W. Jr., and Clark, E. H.: The Effect of Inflation of the Stomach upon the Gastroscopic Picture, Am. J. Digest. Dis. **7**:418, 1940.

89. Benedict, E. B.: Indications for Gastroscopy, New England J. Med. **223**: 925, 1940.

90. Jones, C. M.: Clinical Evaluation of Gastritis, Am. J. Digest. Dis. **8**:205, 1941.

91. Flexner, J., and Fleishman, A.: Analysis of Two Hundred and Fifty-Six Gastroscopies Performed at Bellevue Hospital, Am. J. Digest. Dis. **7**:323, 1940.

the gastric mucosa. Ruffin and his collaborators,⁹² on the basis of over 540 gastroscopic examinations, state that there are no characteristic symptoms and no correlation between the patient's complaints and the gastroscopic picture. Both of these articles are worth perusal in order to attempt a judicious evaluation of the diagnostic possibilities of gastroscopy.

A gastroscopic study of the anatomic changes underlying anacidity was made by Schindler and his collaborators⁹³ on a group of 120 patients with histamine-proved anacidity. Gross anatomic lesions, varying from diffuse inflammatory involvement of the gastric mucosa of all types to patchy areas of gastric atrophy, were said to be present in all except 5 patients. The study includes observations on patients with pernicious anemia or malignant gastric tumor and on patients who had been subjected to a major gastric operation or prolonged roentgen irradiation of the stomach. For the most part, it would appear that atrophic changes were the end results, but these frequently followed previous inflammatory disturbances. The lesions observed in those patients who had been subjected to irradiation of the stomach are of particular interest inasmuch as they range from a mild, transient, superficial type to constant atrophic gastritis.

Moersch and Walters⁹⁴ join other authors in stressing the importance of gastroscopic observations in cases of gastric distress following operations on the stomach. They examined 100 patients in whom such a disturbance developed after gastric operation. Contrary to the statement that gastritis occurs in practically all stomachs after operation, in only one third of the cases of persistent dyspepsia was there gastroscopic evidence of disease. The symptoms in many instances were purely functional, and in a few cases it was thought that demonstrable gastritis had probably existed before the operation. Again, it may be pointed out that only after numerous careful observations will it be possible to give a proper clinical evaluation of what is seen through the gastroscope. This is particularly true when one contrasts the article just mentioned with one by Schindler,⁹⁵ also on gastroscopic examina-

92. Ruffin, J. M.; Brown, I. W. Jr., and Clark, E. H.: The Occurrence of Gastritis as Diagnosed by Gastroscopy in Gastric Neurosis, *Am. J. Digest. Dis.* **7**:414, 1940.

93. Schindler, R.; Nutter, P. B.; Groom, H. E., and Palmer, W. L.: Anatomic Foundations of Anacidity: Gastroscopic Study, *Arch. Int. Med.* **66**:1060 (Nov.) 1940.

94. Moersch, H. J., and Walters, W.: Gastroscopic Observations in Cases of Gastric Distress Following Operations on Stomach, *Surg., Gynec. & Obst.* **71**: 129, 1940.

95. Schindler, R.: Gastroscopic Observations in Resected Stomachs, *Am. J. Digest. Dis.* **7**:505, 1940.

tion of resected stomachs. This author noted normal mucosa in only 4 out of 54 patients who had had major resections of the stomach for cancer or ulcer.

A careful set of observations on the visible motor activity of the stomach is presented by Schindler and Dailey.⁹⁶ Their detailed description of two normal types of rhythmic activity of the pylorus should prove of real value to all interested in carefully controlled gastroscopy. Of particular interest is their observation of a true sphincteric action, similar to that noted at the pylorus, occurring in an operative stoma.

The occasional difficulty in differentiating between chronic hypertrophic gastritis and gastric carcinoma, pointed out by Schindler and others, is illustrated in several cases reported by Brunn and Rubin.⁹⁷ In this particular group of cases there was no doubt that important information could be obtained by experienced gastroscopists, although at times a final diagnosis could be made only after exploration.

A possibly valuable adjunct to gastroscopic studies in the diagnosis of gastritis is discussed by Mulrooney and Eusterman,⁹⁸ who studied the cellular elements in the gastric contents after an alcohol test meal and related them to the underlying condition. Such studies have previously been made by various authors, such as Bockus and others, and are probably in themselves not of absolute diagnostic importance. The appearance of large numbers of leukocytes seems to be the important finding and strongly suggests an inflammatory process. In addition to their association with malignant lesions, increased leukocyte averages appear to be definitely related to any factor causing stasis, whether it is pyloric stenosis or narrowing of an artificial stoma. At best such a diagnostic method offers only confirmatory evidence.

Although probably of little practical clinical importance, the observations of Freedberg and Barron⁹⁹ are of some interest. In a fairly large number of cases these authors have demonstrated spirochetes (not *Spirochaeta pallida*) in or near benign or malignant gastric ulcerations. The organisms were rarely found in gastric tissue resected for duodenal ulcer unless there were concomitant gastric lesions.

The rarity with which gastric diverticulum occurs is evidenced in a report by Reich,¹⁰⁰ who found only 6 instances in over 19,000

96. Schindler, R., and Dailey, M. E.: Gastroscopic Observations on Gastric Motility, *Am. J. Digest. Dis.* **8**:8, 1941.

97. Brunn, H., and Rubin, L. G.: The Surgical Problem of Chronic Gastritis, *Surg., Gynec. & Obst.* **72**:31, 1941.

98. Mulrooney, R. E., and Eusterman, G. B.: Cytology of Gastric Contents, with Special Reference to Gastritis, *Arch. Surg.* **42**:55 (Jan.) 1941.

99. Freedberg, A. S., and Barron, L. E.: The Presence of Spirochetes in Human Gastric Mucosa, *Am. J. Digest. Dis.* **7**:443, 1940.

100. Reich, N. E.: Gastric Diverticula, *Am. J. Digest. Dis.* **8**:70, 1941.

examinations. Symptoms arising from these lesions, which are usually located near the posterior wall of the cardia on the lesser curvature, are not characteristic, and the diagnosis is at times difficult. Penetrating gastric ulcer and diaphragmatic hernia are the two conditions which may cause confusion in the differential diagnosis.

The problem of gastric cancer properly continues to attract serious attention, and the general attitude of the medical profession toward such a diagnosis is still rather fatalistic. The fact that during a fifteen year period approximately 600,000 people in this country died from this cause alone reveals the magnitude of the problem. All authors agree that early diagnosis is something to be hoped for, but achievement lags far behind. Few of the numerous articles in the year's literature contribute any new information, but many place a proper emphasis on the employment of all diagnostic measures in case of doubt. It is unquestionably true that skilful roentgenologic examination and gastroscopic study have both added excellent diagnostic information with respect to this troublesome problem. Schindler¹⁰¹ has contributed another paper to our knowledge of the subject, and although one may hesitate to accept the rather exact criteria which he lays down for the classification of malignant lesions, close attention to the points he stresses will lead to greater diagnostic skill and more exact confirmation of dubious roentgenologic findings. Among other sources of difficulty in making the diagnosis of gastric cancer are gastric polyps, some of which may be benign. Here, again, gastroscopy can provide important information in differentiating between inflammatory pseudopolyps and those that may become, or already are, malignant. Schindler and McGlone¹⁰² pay particular attention to such lesions.

The importance of suspecting cancer of the stomach is emphasized by McNeer, also,¹⁰³ who summarizes rather completely the literature on gastric cancer in the young. He reports 501 well authenticated cases of this condition in subjects under 31 years of age. While the condition is rare in childhood, after the age of 15 the incidence rapidly increases for each five year period. The author points out that not infrequently what should have been diagnostic roentgenologic evidence was disregarded because of the age of the patient. Examination of the protocols of various cases seems to indicate that the disease in young persons is entirely comparable to its counterpart in older ones in regard to duration, pathologic entities, analysis of gastric contents,

101. Schindler, R.: Early Diagnosis and Prognosis of Gastric Carcinoma, *J. A. M. A.* **115**:1693 (Nov. 16) 1940.

102. Schindler, R., and McGlone, F. B.: Familial Occurrence of Hyperplastic Gastric Polyps, *Arch. Surg.* **41**:1483 (Dec.) 1940.

103. McNeer, G.: Cancer of the Stomach in the Young, *Am. J. Roentgenol.* **45**: 537, 1941.

resectability and prognosis, contrary to nearly all other statements on the subject. This article seems to be one of the more authoritative on this particular condition and is well worth reading in detail.

A somewhat similar article by Macleod and Baird,¹⁰⁴ based on a small group of patients, illustrates the difference in clinical impression that may arise from a study of a limited group of patients. In this particular instance, the point of view expressed regarding the outlook of cancer in younger persons is one of absolute hopelessness. It is highly probable that McNeer's impression, based on a much larger number of cases, is more accurate. There can be little doubt, however, that the presence of a gastric lesion, however small, in a younger person makes imperative adequate medical treatment and continuous observation if exploratory operation is not to be undertaken. Obviously, the only proper attitude is that expressed by Eusterman,¹⁰⁵ who reflects the feeling of all careful internists and all experienced surgeons, namely, that any doubtful gastric lesion must be considered malignant until proved otherwise and that those lesions which are considered benign in spite of normal acidity, size or general appearance must still be kept under suspicion and followed closely. Only by maintaining such an attitude can the inadequacy of present methods¹⁰⁶ for early diagnosis and the insidious onset of the disease, as illustrated by the usual short history, be overcome. If surgical intervention for a gastric lesion is indicated, there can be no doubt that with increasing operative skill and improved preoperative and postoperative care somewhat more hopeful results are being obtained. Priestley's¹⁰⁷ report of a recent study of 10,890 cases in which gastric cancer was diagnosed illustrates this fact. Exploration was performed in approximately 60 per cent of the cases, in about one half of which resection of the stomach was possible. Operative mortality was approximately 5 per cent. In short, with the best of surgical skill, about 25 per cent of patients in whom a diagnosis of gastric cancer is made may hope for possible favorable results, although in only about one third of this series of cases did the patient live for five years or more. In other words, it was found that of the

104. Macleod, J. G., and Baird, R. B.: Carcinoma of Stomach in Young Subjects, *Edinburgh M. J.* **47**:627, 1940.

105. Eusterman, G. B.: Small Carcinomatous Gastric Lesions Simulating Chronic Benign Ulcer: Present Status of Differential Diagnosis and Treatment, *Minnesota Med.* **23**:703, 1940.

106. Abrahamson, R. H., and Hinton, J. W.: Carcinoma of the Stomach: Review of Four Hundred and Forty-Four Cases to Emphasize Inadequacy of Present Methods for Early Diagnosis, *Surg., Gynec. & Obst.* **71**:135, 1940. Bade, H.: Has Roentgenologic Diagnosis Improved the Therapeutic Results in Gastric Cancer? *Fortschr. a. d. Geb. d. Röntgenstrahlen* **62**:114, 1940.

107. Priestley, J. T.: Carcinoma of the Stomach, *Minnesota Med.* **24**:81, 1941.

1,951 patients who survived gastric resection and were traced, 29 per cent lived for five years or longer. Thus, in 6 to 8 per cent of those cases in which the correct diagnosis is made the patient has a real chance of surviving in a cured condition for five years. Such figures are worthy of attention, inasmuch as many members of the medical profession still hesitate to resort to radical surgical measures, although it is apparent that only such measures will ever be effective in reducing the mortality from this common and terribly serious condition.

Search for the cause of cancer still is essentially one of medical speculation. Ewing¹⁰⁸ summarizes the various current concepts and comments critically on the leads thus far obtained that are worthy of study.

Cases of gastric syphilis are not common but occur with sufficient regularity to warrant their inclusion in any discussion of carcinoma of the stomach. Reports by Williams and Kimmelstiel,¹⁰⁹ Parsons¹¹⁰ and Avent¹¹¹ indicate clearly the close similarity between syphilis of the stomach and gastric cancer. In practically every instance the lesion occurs near the pylorus, and nearly always a diagnosis of probable cancer is made on the basis of roentgenologic evidence. The possibility of syphilis of the stomach should always be remembered, especially if positive serologic reactions are associated with inadequate anti-syphilitic treatment. Most intensive and specific treatment should be initiated, and at times this will successfully control the situation. In most instances, however, enough scarring and deformity have taken place that subtotal gastrectomy is indicated, and favorable results should be expected. Gastroenterostomy was attempted in 1 of the cases reported and was entirely unsuccessful.

A further cause of confusion in the roentgenologic diagnosis of gastric carcinoma is a similar granulomatous process, tuberculosis of the stomach. Sullivan and associates,¹¹² Ackermann¹¹³ and Connolly¹¹⁴ all report cases of this condition. In Sullivan's series, only 2 cases of involvement of the stomach were noted in 544 cases of tuber-

108. Ewing, J.: Etiological Indications of Early Gastric Cancer, *Rev. Gastroenterol.* **7**:305, 1940.

109. Williams, C., and Kimmelstiel, P.: Syphilis of the Stomach, *J. A. M. A.* **115**:578 (Aug. 24) 1940.

110. Parsons, P. B.: Gastric Syphilis, *Radiology* **36**:371, 1941.

111. Avent, C. H.: Syphilis of the Stomach Necessitating Total Gastrectomy, *Surgery* **9**:571, 1941.

112. Sullivan, R. C.; Francona, N. T., and Kirshbaum, J. D.: Tuberculosis of Stomach, *Ann. Surg.* **112**:225, 1940.

113. Ackermann, A. J.: Roentgenological Study of Gastric Tuberculosis, *Am. J. Roentgenol.* **44**:59, 1940.

114. Connolly, A. E.: Tuberculosis of the Stomach, *Brit. J. Radiol.* **13**:351, 1940.

culosis, and 1 other case was encountered among 75,000 surgical specimens. The condition is thus rare, but, like syphilis, the disease usually produces its lesions in the region of the pyloric antrum, although it may extend into the duodenum. In cases of the ulcerative type the usual roentgenologic picture is that of a narrowed antrum, with circular marginal defects and mucosal changes characteristic of superficial ulcer. One case of successful treatment by resection is reported.

Congenital pyloric obstruction is of interest inasmuch as it may produce minor changes that carry over into adult life, although, of course, its primary importance lies in its occurrence in infants. Tour-off and Sussman¹¹⁵ report an unusual manifestation of congenital pyloric deformity due to a complete pyloric septum of mucous membrane in an infant. Surgical intervention was successful. It is of interest that other members of the family suffered from congenital abnormalities. The usual manifestations of pyloric stenosis in infants have been thoroughly described, but Ford, Brown and McCreary¹¹⁶ raise an interesting point regarding its cause in their report of this condition in 2 pairs of male twins of monozygotic origin. They suggest twinning as an etiologic factor, since more than twice the expected number of twins occurred in a series of 436 patients with pyloric stenosis.

The usual controversy regarding medical and surgical treatment of this condition still exists. Proponents of medical treatment attempt to produce pyloric relaxation by various antispasmodics, and favorable results are reported by Haas,¹¹⁷ although he admits that in some instances surgical intervention is indicated. In the last ten years the mortality in 2,840 cases in which surgical treatment was given was 6 per cent, whereas in the same period the mortality with medical treatment in 1,218 cases was 7.8 per cent. Such figures, however, are somewhat misleading, and inasmuch as surgical mortality among properly treated patients has been reported to be as low as 3 per cent for reasonably large groups of infants, there can be little doubt that medical treatment should be abandoned if it is not rapidly followed by satisfactory results. Nuboer¹¹⁸ reports 2 interesting cases in adults. Resected pyloric tissue revealed no evidence of previous ulceration and

115. Touroff, A. S. W., and Sussman, R. M.: Congenital Prepyloric Membranous Obstruction in Premature Infant, *Surgery* 8:739, 1940.

116. Ford, N.; Brown, A., and McCreary, J. F.: Evidence of Monozygosity and Disturbances of Growth in Twins with Pyloric Stenosis, *Am. J. Dis. Child.* 61:41 (Jan.) 1941.

117. Haas, S. V.: Congenital Hypertrophic Pyloric Stenosis, *J. Mt. Sinai Hosp.* 7:411, 1941.

118. Nuboer, J. F.: Hypertrophic Pyloric Stenosis in Adults, *Nederl. tijdschr. v. geneesk.* 84:1687, 1940.

appeared to indicate that a minor degree of what may well have been a congenital condition had existed for some years. A most unusual cause of pyloric obstruction is that reported by Krieg,¹¹⁹ in which heterotopic pancreatic tissue produced symptoms of ulcer, together with the clinical picture of pyloric stenosis.

The relation between the stomach and hematopoiesis is thoroughly established. This subject is of particular interest in the present review in its relation to the problem of gastrectomy. Individual instances of pernicious anemia secondary to gastrectomy are occasionally reported but are relatively rare. In an experimental study of the effects of gastrointestinal resection in swine on the antianemic potency of liver Geiger and his associates¹²⁰ tested the theory of storage of the anti-anemic principle in the liver by removing the stomach. The anti-pernicious anemia principle was progressively depleted, and the potency of the liver was completely exhausted within six months. Similar results obtained when the stomach was isolated but not removed suggested that the effective factor results from gastric digestion rather than from an internal secretion of the stomach and that the liver stores, or elaborates and stores, a product furnished by the stomach. Similarly, extirpation of the duodenum in swine diminished the liver's content of the antianemic principle, indicating that the duodenum is also a true source of Castle's intrinsic factor. In spite of the acknowledged importance of the stomach in controlling normal hematopoiesis, it is surprising that subtotal, or even total, resection of the stomach in human beings only occasionally results in serious anemia, either of the Addisonian or of the hypochromic, iron deficiency type. The entire question of gastrectomy in relation to the production of anemia is reviewed by Jones¹²¹ and by Ivy.¹²² It is obvious that reasonable measures taken postoperatively, with careful attention to nutritional factors, are all that is needed to prevent anemia in gastrectomized persons. The exact portion of the stomach responsible for the chief hematopoietic activity is still not known, although the preponderance of evidence indicates the pars pylorica. Inasmuch as the results of animal experiments are at times contradictory, the observations of

119. Krieg, E. G.: Heterotopic Pancreatic Tissue Producing Pyloric Obstruction: A Review and Case Report, *Ann. Surg.* **113**:364, 1941.

120. Geiger, A. J.; Goodman, L. S., and Claiborn, L. N.: Effects of Gastro-Intestinal Resections in Swine on Antianemic Potency of Liver: Observations on Nature and Sources of Material Effective in Pernicious Anemia, *Yale J. Biol. & Med.* **13**:259, 1940.

121. Jones, C. M.: The Problem of Gastrectomy and the Anemias, *Am. J. Digest. Dis.* **7**:502, 1940.

122. Ivy, A. C.: The Effects of Gastrectomy in Animals, *Am. J. Digest. Dis.* **7**:500, 1940.

Schenken, Stasney and Hall ¹²³ are of some importance. These authors compared the effect of an extract prepared from the liver of a patient with scirrhus cancer of the pars pylorica with that of an extract similarly prepared from the liver of a patient with cancer of the stomach at a higher level. The effect of the latter extract on patients with pernicious anemia was entirely satisfactory, while no remission was obtained after the use of the liver extract from the patient with pyloric cancer.

Peptic Ulcer.—The developmental factors in peptic ulcer have always included body build. A good statistical presentation of this phase of the ulcer problem is made by Robinson and Brucer,¹²⁴ who measured body build, weight and blood pressure in 250 men with peptic ulcer and in a control group of approximately 7,500 normal men. The results confirm the generally accepted opinion that the patient with ulcer differs in every measure except height. He tends to be of normal or less than normal weight; the circumference of the chest and that of the abdomen are less than normal, and the systolic and diastolic blood pressures are at a low level of normal range.

Although it is fairly generally accepted that a close relation exists between intracranial lesions and the occurrence of peptic ulcer, the histologic studies of Boles and Riggs ¹²⁵ are of some importance in focusing attention on the neurogenic factors in the production of ulcer. These authors studied 15 cases of acute gastric ulcer associated with primary intracerebral disease and found no pathologic difference between this type of ulcer and acute ulcer in the absence of such disease. They view the ulcers as focal expressions of circulatory changes secondary to abnormal stimulation of the central vegetative nervous system. Support for such a conception is also found in Lium's experimental observations, already referred to. Removal of the prevertebral ganglions in dogs was followed by ulcerations of the stomach and intestine. Reference has already been made to the mucosal lesions in shock described by Penner and his associates, and one must be extremely skeptical who does not assign an important role to neurogenic and resulting circulatory disturbances in the initiation of ulcer.

The study of experimental ulcer in animals still continues. Swan ¹²⁶ made further observations on cinchophen-produced ulcers in dogs

123. Schenken, J. R.; Stasney, J., and Hall, W. K.: The Antianemic Principle in the Human Liver in Carcinomas of the Stomach and Cecum, *Am. J. M. Sc.* **200**:11, 1940.

124. Robinson, S. C., and Brucer, M.: The Body Build of the Male Ulcer Patient, *Am. J. Digest. Dis.* **7**:365, 1940.

125. Boles, R. S., and Riggs, H. E.: Neurogenic Factors in the Production of Acute Gastric Ulcer, *J. A. M. A.* **115**:1771 (Nov. 23) 1940.

126. Swan, H.: Effect of Cholecystogastrostomy on Cinchophen-Produced Ulcer in Dogs, *Arch. Surg.* **41**:569 (Sept.) 1940.

to determine the effect of cholecystogastrostomy with ligation of the common duct. As might have been predicted, no significant difference in the incidence of gastrointestinal ulceration was to be noted in this group as compared with incidence in the control group. However, Carr and Foote¹²⁷ observed that simple ligation of the common bile duct, with complete lack of delivery of bile into the gastrointestinal tract, did cause gastroduodenal ulceration in more than half of their experimental animals. Such a finding is of some clinical importance, since it is possible that spontaneous hemorrhage following prolonged obstruction of the common bile duct in human beings may conceivably be due to gastroduodenal ulceration independent of any alteration in prothrombin values.

Confirmation of previous results on the favorable effect of the injection of chorionic gonadotropin into Mann-Williamson dogs is to be found in the experimental results of Broad and Berman.¹²⁸ Inasmuch as Sandweiss and his collaborators failed to obtain such results in dogs with experimentally produced cinchophen ulcers, one must still be skeptical as to the effectiveness of chorionic gonadotropin. Further studies on the effect of this substance are certainly warranted.

That increased gastric acidity exists in the presence of duodenal ulcer has been known for a long time and is clearly confirmed by the careful studies of Bloomfield and his collaborators.¹²⁹ They also produce acceptable evidence that as far as gastric acid secretion is concerned values are distinctly higher in the case of duodenal ulcer than they are in the case of gastric ulcer. That large quantities of gastric acid enter the duodenum and that the neutralizing mechanism of this portion of the small intestine is necessarily disturbed in the presence of duodenal ulcer were confirmed by Kearney and his colleagues.¹³⁰ These findings were to have been expected and are of importance clinically, but the emphasis placed by Bloomfield on the diagnostic value of analyses of basal gastric secretion seems to be unwarranted.

127. Carr, J. L., and Foote, F. S.: The Genesis of Peptic Ulcer in Dogs Following Ligation of the Common Bile Ducts, *Surg., Gynec. & Obst.* **72**:198, 1941.

128. Broad, G. G., and Berman, L. G.: Treatment of Experimental Mann-Williamson Ulcers with Anterior Pituitary-Like Hormone (Antuitrin-S), *Am. J. Digest. Dis.* **8**:27, 1941.

129. Bloomfield, A. L.; Chen, C. K., and French, L. R.: Basal Gastric Secretion as a Clinical Test of Gastric Function with Special Reference to Peptic Ulcer, *J. Clin. Investigation* **19**:863, 1940.

130. Kearney, R. W.; Comfort, M. W., and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study, *J. Clin. Investigation* **20**:221, 1941.

It is still true that expert roentgenography supersedes all other methods as the most efficient means of diagnosing peptic ulcer.

To those interested in the histologic aspects of ulcer Rabinovitch and associates¹³¹ present an excellent illustrated review of 200 cases. The demonstration of inflammatory changes about the nerve fibers and ganglions undoubtedly helps to visualize the pain mechanism involved in ulcer.

In an article on peptic ulcer by Dwyer and co-workers¹³² two points are worthy of comment. In a series of over 1,000 cases the ratio of incidence of duodenal ulcer to that of gastric ulcer was approximately 9 to 1, a somewhat higher incidence for the former than is usually reported. Of greater clinical importance is their statement that the present efficiency of roentgenographic diagnosis will demonstrate duodenal ulcer in approximately 17 per cent of patients whose history is completely atypical of this common condition.

Cases of peptic ulcer in children continue to be reported, and it is apparent that this condition should be suspected more frequently than it is at present. The actual frequency with which this condition is encountered is indicated by Burdick,¹³³ who reports 8 instances in over 21,000 admissions to the Children's Hospital. Both he and Moore¹³⁴ stress one important point, namely, that the characteristic story of hunger pain relieved by food does not occur in most instances, and both authors agree that epigastric tenderness tends to be poorly localized or to be completely absent. It is obvious that continued bouts of abdominal pain in the young warrant adequate roentgenologic studies. Logan and Walters¹³⁵ report 1 instance of gastric ulcer in a child among 2,000 cases of ulcer of the stomach, and Quinn¹³⁶ records 2 cases of ruptured gastric ulcer and 1 of ruptured duodenal ulcer among 8 newborn infants.

The importance of peptic ulcer in the aged is indicated in a review by Mulsow,¹³⁷ who notes that of patients who die of peptic ulcer about

131. Rabinovitch, J.; Pines, B., and Teicher, I.: Pathogenesis and Pathologic Changes in Peptic Ulcer and Production of Pain, *Arch. Int. Med.* **67**:620 (March) 1941.

132. Dwyer, M. F.; Blackford, J. M.; Cole, W. S., and Williams, R. H.: Peptic Ulcer: A Review of 1,033 Cases and a Follow-up Study of the Patients Diagnosed Between Ten and Twenty Years Ago, *Radiology* **36**:217, 1941.

133. Burdick, W. F.: Peptic Ulcer in Children: Report of Ten Cases, *J. Pediat.* **17**:654, 1940.

134. Moore, O. M.: Peptic Ulcer in Children, *Canad. M. A. J.* **44**:462, 1941.

135. Logan, G. B., and Walters, W.: Chronic Gastric Ulcer in Childhood, Treated Surgically, *Ann. Surg.* **113**:260, 1941.

136. Quinn, A. G.: Report of Two Ruptured Gastric Ulcers and One Ruptured Duodenal Ulcer in Three Newborn Infants, *South. M. J.* **33**:1171, 1940.

137. Mulsow, F.: Peptic Ulcer of the Aged, *Am. J. Digest. Dis.* **8**:112, 1941.

one third are beyond the age of 60 years, another third are in the sixth decade and the remainder are below the age of 50. The literature also reveals that massive hemorrhage is nearly twice as frequent in persons who are more than 60 years old.

The effect of war conditions on the activation of peptic ulcer is of current interest and is emphasized in articles by Allison¹³⁸ and Tillisch¹³⁹ and in an editorial comment in the *Canadian Medical Association Journal*.¹⁴⁰ Allison, on the basis of studies of men in the Royal Navy, states that peptic ulcer appears to be the only serious condition of dyspepsia in the present war, although its occurrence in the navy is perhaps not so frequent as in the army. He properly stresses the psychologic factors that play a part in wartime. The importance of disability in the armed forces, particularly under fighting conditions, is further stressed by the Canadian editorial, in which it is stated that in nearly one eighth of the men evacuated to base hospitals from the expeditionary force to France the debilitating condition was given the primary diagnosis of gastric or duodenal disease. The urgent necessity for the elimination of patients with ulcer from certain phases of war activity and for rejection by boards of selection of persons with suspected ulcer is emphasized by Tillisch in a report of a case of serious hemorrhage from a duodenal ulcer in a pilot in flight.

Perforation of peptic ulcer is of common occurrence. Cohn¹⁴¹ considers particularly the problem of repeated perforation. Four per cent of 300 patients operated on for perforated peptic ulcer presented a history of repeated perforation, which suggests that gastric resection is the operation of choice for this particular group of patients. The simultaneous perforation of a duodenal and a gastric ulcer is unusual enough to warrant reference to the case reported by Stobie.¹⁴² The importance of the ability to make an accurate preoperative diagnosis of perforated peptic ulcer is apparent. Thaxter¹⁴³ and Williams and Hartzell¹⁴⁴ discuss the diagnostic aid that can be gained by adequate roentgenologic examination in all cases of possible perforated viscera. In 80 per cent

138. Allison, R. S.: Peptic Ulcer in the Royal Navy, *Lancet* **1**:596, 1941.

139. Tillisch, J. H.: Hemorrhage from Duodenal Ulcer in a Pilot While Flying, *Proc. Staff Meet., Mayo Clin.* **16**:209, 1941.

140. Peptic Ulcer—The Major Disability of Wartime, editorial, *Canad. M. A. J.* **44**:508, 1941.

141. Cohn, R.: Repeated Perforations of Peptic Ulcers, *Surgery* **9**:688, 1941.

142. Stobie, G. H.: Simultaneous Perforation of Duodenal and Gastric Ulcer, *Canad. M. A. J.* **44**:54, 1941.

143. Thaxter, L. T.: Spontaneous Pneumoperitoneum in Perforated Peptic Ulcer (Roentgen-Ray Analysis of Forty-Four Cases), *Am. J. Roentgenol.* **44**:853, 1940.

144. Williams, A. J., and Hartzell, H. V.: Perforated Peptic Ulcer: A More Accurate Method of Roentgen Diagnosis, *Surg., Gynec. & Obst.* **71**:606, 1940.

of Thaxter's cases there was roentgenologic evidence of a spontaneous pneumoperitoneum localized beneath either the right or the left side of the diaphragm. A somewhat similar percentage was obtained in a much larger group (358 cases) by Williams and Hartzell. These authors also discuss the importance of taking roentgenograms with the patient standing erect and lying on the left side. A careful comparison of results indicates clearly that in this particular group of cases pneumoperitoneum was demonstrated in about 75 per cent in which the roentgenogram was made with the patient in an upright position. In those instances in which a left lateral decubital position was employed, practically 90 per cent of the roentgenograms showed the presence of air in the abdominal cavity. A follow-up study by Ross¹⁴⁵ brings out an important consideration bearing on the mortality of perforated ulcer. Half, or 8 per cent, of the fatalities in the author's series, were definitely associated with the existence of serious intercurrent disease. The obvious importance of streptococcic peritoneal infection in association with a perforated peptic ulcer is stressed by Griswold and Antoncic,¹⁴⁶ who urge equally obvious therapy, the employment of sulfanilamide or one of its derivatives.

The diagnostic problems inherent in the presence of hematemesis are well known. In reviewing the differential diagnosis of gastric hemorrhage, Ask-Upmark¹⁴⁷ mentions a point of minor importance, namely, that an increase in blood nonprotein nitrogen is inconclusive evidence of renal insufficiency so long as blood is present in the digestive tract. This point may need to be considered when one is confronted with the occasional uremic patient in whom gastric hemorrhage is due to renal failure. One diagnostic point omitted from an otherwise complete review was the possible use of splenic percussion in making the diagnosis of cirrhosis of the liver as the cause of hemorrhage. Inasmuch as careful examination of the abdomen is more or less contraindicated in the presence of massive hemorrhage, such a procedure may at times give the most direct evidence of the underlying cause of trouble.

In a further study of fatal hemorrhage from peptic ulcer, Blackford and Williams¹⁴⁸ review the causes of death in Seattle on the basis of vital statistics. Little new is added, but two points are worthy of repeti-

145. Ross, J. C.: Perforated Peptic Ulcer: Review of One Hundred and Seventy-Five Personal Cases, *Brit. M. J.* **2**:665, 1940.

146. Griswold, R. A., and Antoncic, R. F.: Perforated Peptic Ulcer, *Ann. Surg.* **113**:791, 1941.

147. Ask-Upmark, E.: Differential Diagnosis in Gastric Hemorrhage, *Acta chir. Scand.* **84**:30, 1940.

148. Blackford, J. M., and Williams, R. H.: Fatal Hemorrhage from Peptic Ulcer: One Hundred and Sixteen Cases Collected from Vital Statistics of Seattle During the Years 1935-1939 Inclusive, *J. A. M. A.* **115**:1774 (Nov. 23) 1940.

tion: Ninety-seven per cent of all the fatalities due to hemorrhage from ulcer occurred in patients over 45 years of age. This fact needs continued emphasis, particularly when one considers the possible surgical approach to the emergency. The second point is that nearly 80 per cent of all fatalities occurred during the first hemorrhage. In spite of the immense surgical risk, the authors frankly advocate surgical intervention early in the treatment of this condition.

Azotemia in association with gastrointestinal hemorrhage is now known to be rather constant. In animal experiments, Chunn and Harkins¹⁴⁹ followed the progressive changes in the blood of animals to which citrated beef blood had been administered intragastrically. The blood urea nitrogen became elevated within three to eight hours, reached a maximum concentration between five and a half and nineteen hours after administration of the blood, depending on the amount given and on the number of doses, and returned to a normal level in six to nineteen and a half hours. They state that the dogs were not starved, dehydrated, markedly anemic, hypochloremic or in shock. They suggest the term "alimentary azotemia," inasmuch as elevation of urea nitrogen is undoubtedly dependent on the nitrogenous material contained in the blood ingested. In a second article,¹⁵⁰ these authors state that the degree of azotemia under such circumstances is of considerable prognostic significance in human beings, the highest values being associated with the highest mortality. Johnson¹⁵¹ differs strongly on the basis of the most careful clinical observations that have yet been made. He noted, as have all other observers, a marked rise in the urea nitrogen of the blood in cases of gross hemorrhage, but only when there was a temporary or permanent reduction in renal function. He also noted that no changes occurred in the serum chloride or in the carbon dioxide-combining power of the plasma. Johnson believes that whole blood in the upper portion of the gastrointestinal tract is digested and absorbed and results in the formation of urea. He states that the pathogenesis of the azotemia depends on a rate of urea formation which is in excess of the rate at which urea can be excreted by the kidneys and presents adequate evidence to warrant this hypothesis. He states clearly that there is no definite correlation between the degree of azotemia and the prognosis for recovery. The absence of azotemia in some patients with massive hemor-

149. Chunn, D. F., and Harkins, H. N.: *Experimental Studies on Alimentary Azotemia: I. Role of Blood Absorption from the Gastrointestinal Tract*, *Surgery* 9:695, 1941.

150. Chunn, C. F., and Harkins, H. N.: *Alimentary Azotemia: A Clinical Syndrome Occurring as a Part of the Bleeding Peptic Ulcer Complex*, *Am. J. M. Sc.* 201:745, 1941.

151. Johnson, J. B.: *The Pathogenesis of Azotemia in Hemorrhage from the Upper Gastro-Intestinal Tract*, *J. Clin. Investigation* 20:161, 1941.

rhage into the upper portion of the gastrointestinal tract may be explained by the presence of normal renal function. In them the rate at which urea is excreted quickly equals the increased rate of urea production. It is highly probable that his conclusions are sound and that attempts to read too much into the prognostic significance of an interesting laboratory finding are unwarranted.

Somewhat in contrast to the preceding are the facts presented by Bick and Wood ¹⁵² in a discussion of the biochemical changes associated with hemorrhage from the stomach and duodenum. They were able to demonstrate what is undoubtedly true in certain instances—that patients with profuse gastric or duodenal hemorrhage suffer not only from anemia but from depleted blood volume, starvation, dehydration, chloride and protein deficiency, renal dysfunction and acidosis. Obviously, such a summary is too inclusive in many cases, but it indicates the therapeutic considerations that frequently have to be recognized.

The possible factors influencing hemorrhage from the gastrointestinal tract were studied by Moss and his collaborators.¹⁵³ They present rather conclusive evidence that vitamin C deficiency bears no relation to the hemorrhage in most cases but were unable to demonstrate any consistent alteration in the various factors entering into the clotting mechanism that might be important.

Amaurosis following severe hemorrhage has been recognized since the time of Hippocrates, but it certainly is a rare sequel to severe gastric hemorrhage. Such a case is reported by Bamford and Barber,¹⁵⁴ in which complete blindness followed within three weeks of a large hemorrhage from an ulcer. Another queer sequel of massive hemorrhage from the gastrointestinal tract is that reported by Ewertsen and Meulengracht,¹⁵⁵ who comment on 4 cases of gout following hematemesis and melena. Because of these, studies were made in other cases of massive hemorrhage, and it was found that there was an increased excretion of uric acid in the urine after the hemorrhage, which the authors attributed to the increased regeneration of blood and the increased liberation and disintegration of normoblast nuclei.

152. Bick, M., and Wood, I. J.: Some Observations on Biochemical Changes Associated with Hemorrhage from Stomach and Duodenum, *M. J. Australia* **1**:104, 1941.

153. Moss, H. K.; Schiff, L.; Stevens, R. J., and Rich, M. L.: The Blood in Cases of Hematemesis and Melena with Reference to Factors Influencing Hemorrhage, *Am. J. Digest. Dis.* **7**:490, 1940.

154. Bamford, C. H., and Barber, H.: Blindness Following Hematemesis, *Lancet* **2**:715, 1940.

155. Ewertsen, H., and Meulengracht, E.: Attacks of Arthritis Urica and Increased Excretion of Uric Acid in Patients with Hematemesis and Melena, *Ugesk. f. læger* **102**:1157, 1940.

The treatment of choice for massive hemorrhage from peptic ulcer still lies between medical and surgical measures in selected cases. Stone¹⁵⁶ reflects the view of many that radical surgical procedure is indicated for older patients but admits frankly that the value of early surgical intervention will not become apparent until comparative figures are available for the age group in question. He believes that at present the chances of surviving radical surgical procedure will be less than the probable two in three chances of survival following medical treatment. Whether these figures are exact is beside the point; it is obvious that the surgeon must be willing to accept a high risk if he hopes to reduce the already high mortality figures incident to gross bleeding in patients over 50 years of age.

Medical measures include particularly the use of colloidal aluminum hydroxide or a selected diet, such as that outlined by Andresen and Meulengracht. Woldman¹⁵⁷ claims to have reduced the mortality in emergency cases of massive hemorrhage from 28 to 2 per cent by the continuous administration of colloidal aluminum hydroxide. Various authors report successful use of the Meulengracht regimen, although no additional figures of value are presented. It is obvious that strict medical measures are efficacious, except for the small group of older patients in whom surgical treatment may have to be considered. Starvation treatment in the hands of most physicians has little to recommend it in the face of results obtained by the methods just suggested.

Further studies on the effect of various antacids in the control of gastric acidity and the treatment of peptic ulcer continue to appear. Kirsner,¹⁵⁸ in contrasting the values of magnesium carbonate, a combination of calcium carbonate and magnesium carbonate, tribasic magnesium phosphate, tribasic calcium phosphate and magnesium trisilicate, places these antacids in this order as regards their ability to control gastric acidity. In somewhat similar studies, Flexner and Kniazuk¹⁵⁹ obtained evidence that the greatest rise in p_H is caused by Sippy A powder (sodium bicarbonate and magnesium oxide) and magnesium peroxide, 25 per cent (magnesium superoxol), but that this rise is of lesser duration than that produced by a suspension of aluminum

156. Stone, C. S., Jr.: Treatment of Massive Hemorrhage from Peptic Ulcer, *West. J. Surg.* **48**:564, 1940.

157. Woldman, E. E.: The Treatment of Massive Gastro-Duodenal Hemorrhage by the Continuous Administration of Colloidal Aluminum Hydroxide: A Report of One Hundred and Forty-Four Cases, *Am. J. Digest. Dis.* **8**:39, 1941.

158. Kirsner, J. B.: A Further Study of the Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents, *Am. J. Digest. Dis.* **8**:53, 1941.

159. Flexner, J., and Kniazuk, M.: A Method for the Continuous Recording of Gastric p_H in Situ: III. Evaluation of the Efficacy of Certain Antacids, *Am. J. Digest. Dis.* **8**:45, 1941.

hydroxide. Magnesium trisilicate and sodium bicarbonate produced rises of relatively short duration. Wilkinson and Commanduras,¹⁶⁰ in a study of over 300 cases of peptic ulcer, conclude that much more effective results are produced by preparations of aluminum hydroxide than by Sippy powders. Collins and his collaborators¹⁶¹ claim equally satisfactory results from the use of aluminum hydroxide in a large series of cases of ulcer. They emphasize, however, that a well balanced diet given according to certain well accepted regulations is equally important. Schiffrin and Komarov¹⁶² demonstrate that various aluminum preparations inactivate pepsin even at a p_H as low as 1.0, a result not obtained with magnesium trisilicate. Aluminum hydroxide seems to be the most effective.

The effects of the prolonged administration (seven to eight months) of aluminum hydroxide on the acid-base balance and on renal function were studied by Kirsner,¹⁶³ who found no change in the blood electrolytes in any instance and no abnormality in blood urea nitrogen or in urea clearance. The use of aluminum hydroxide in 3 cases in which there was a marked reduction in renal function subsequent to alkalosis was followed by the maintenance of a normal acid-base balance and by gradual improvement in the urea clearance. Such observations would seem to be of maximum importance in relation to antacid therapy.

Fauley and his collaborators¹⁶⁴ report extremely careful studies on aluminum phosphate in the therapy of peptic ulcer and the effect of aluminum hydroxide on absorption of phosphate. Both in Mann-Williamson dogs and in human beings the results show that a negative phosphorus balance may be produced by aluminum hydroxide when the diet is low in phosphorus. Aluminum hydroxide alone did not prevent the development of jejunal ulcer in Mann-Williamson dogs. On the other hand, the administration of aluminum phosphate gel prevented the development of ulcer in all but 3 of 23 similarly prepared animals. Aluminum phosphate gel therapy caused complete healing in 9 of 10 animals in which an ulcer had already developed, a striking result.

160. Wilkinson, S. A., and Commanduras, P. D.: The Treatment of Peptic Ulcer with Aluminum Hydroxide: A Two-Year Study, *New England J. Med.* **223**:972, 1940.

161. Collins, E. N.; Pritchett, C. P., and Rossmiller, H. R.: The Use of Aluminum Hydroxide in the Treatment of Peptic Ulcer; A Follow-Up Study of Two Hundred and Forty-Six Cases, *J. A. M. A.* **116**:109 (Jan. 11) 1941.

162. Schiffrin, M. J., and Komarov, S. A.: The Inactivation of Pepsin by Compounds of Aluminum and Magnesium, *Am. J. Digest. Dis.* **8**:215, 1941.

163. Kirsner, J. B.: The Effect of Aluminum Hydroxide on the Acid-Base Balance and on Renal Function, *Am. J. Digest. Dis.* **8**:160, 1941.

164. Fauley, G. B.; Freeman, S.; Ivy, A. C.; Atkinson, A. J., and Wigodsky, H. S.: Aluminum Phosphate in the Therapy of Peptic Ulcer: Effect of Aluminum Hydroxide on Phosphate Absorption, *Arch. Int. Med.* **67**:563 (March) 1941.

Aluminum phosphate gel was administered to a group of patients with ulcer, with results that seem to promise as great effectiveness from this preparation as from any other antacid. The experimental results, the authors point out, do not necessarily imply that aluminum phosphate gel is superior to aluminum hydroxide gel for the management of peptic ulcer in man, except in the presence of relative or absolute deficiency of pancreatic juice, diarrhea or a low phosphorus diet.

The urinary excretion of silica following the administration of magnesium trisilicate was studied by Heffner and his associates¹⁶⁵ in patients with ulcer and in patients with achlorhydria (pernicious anemia). During a four day experimental period in which the drug was administered orally the urinary excretion of silica increased appreciably. Those patients with achlorhydria had the greatest excretion, the absorption of silica from the intestine probably being dependent on its solubility in the alkaline intestinal contents. Only a small proportion of the silica contained in magnesium trisilicate was absorbed, however, and none of the patients showed any toxic symptoms.

Kirsner and Palmer¹⁶⁶ report that in 32 of 105 patients receiving calcium carbonate in the treatment of peptic ulcer alkalosis developed within three days after the onset of treatment. The carbon dioxide-combining power and the p_H of the blood were elevated, and the serum chlorides were markedly lowered. The urea clearance decreased in 25 patients during alkalosis, with a rise in urea nitrogen to a peak of 67.6 mg. in 1 case. Albuminuria was noted in 2 cases, and albumin, casts and red blood cells occurred in the urine in a third case. Recovery of normal renal function after the discontinuance of treatment was rapid in all but 3 cases, in which recovery occurred only after one, three and six months, respectively. The authors attributed the alkalosis to chloride deficiency and consequent dehydration. When necessary it could be combated successfully by the administration of adequate quantities of sodium chloride and fluid. The authors point out, however, that when alkalosis appears the most obvious therapeutic measure is to stop the use of alkali.

The changes in the blood secondary to pyloric stenosis and prolonged vomiting are well known. Pérez-Castro¹⁶⁷ observed deposits of calcium

165. Heffner, R. R.; Page, R. C., and Frey, A.: Urinary Excretion of Silica in Humans Following Oral Administration of Magnesium Trisilicate: II. In Five Patients with Peptic Ulcer and Three with Pernicious Anemia, *Am. J. Digest. Dis.* **8**:219, 1941.

166. Kirsner, J. B., and Palmer, W. L.: The Role of Chlorides in Alkalosis Following Administration of Calcium Carbonate, *J. A. M. A.* **116**:384 (Feb. 1) 1941.

167. Pérez-Castro, E.: Nephrosis Due to Calcium Deposits in Pyloric and Duodenal Stenosis, *Semana méd. españ.* **3**:1016, 1940.

in the lumens of the uriniferous tubules of the kidneys, either with flattening or with complete disappearance of the tubular epithelium. The author is undoubtedly correct in believing that the renal lesions are associated with the hypochloremia encountered in such conditions and with the azotemia, which are only the aggravated stages of the functional-morphologic changes in the kidneys.

The literature on the surgical treatment of ulcer presents nothing new. A report by Walters¹⁶⁸ is worthy of comment inasmuch as it concerns one of the types of peptic ulcer which is most difficult to treat, namely, that in close proximity to the cardiac orifice of the stomach. Of nearly 550 gastric lesions which were operated on, one-seventh were found to be at or higher than a point midway between the angle of the stomach and the esophagus. About one half of the lesions so situated proved to be benign gastric ulcers. Partial gastric resection was performed in two thirds of the cases of benign ulcer, and in all but 1 of 34 cases of carcinoma at this level some form of gastric resection was done, with but 5 deaths. The mortality of this difficult gastric procedure was extremely low, partial or subtotal gastrectomy being the usual operation of choice. Gastroenterostomy was performed if the patient's condition did not warrant a more serious operation or if the lesion was too close to the esophagus to permit of any other procedure. Frequently the high gastric lesion appeared higher in the roentgenogram than was actually observed at operation. The difficulty of differentiating malignant from benign ulcerative processes in the cardia by roentgen examination is reemphasized.

The failure of excision of the pylorus and antrum in man to produce approximate or complete achlorhydria was demonstrated experimentally in animals by Wangensteen and his collaborators.¹⁶⁹ They doubt the validity of Edkins' hypothesis of a pyloric and antral hormone which controls the gastric phase of gastric secretion and believe that their results constitute adequate evidence that subtotal gastric resection is the most logical surgical procedure in the treatment of peptic ulcer.¹⁹

The not infrequent recurrence of ulcer after various forms of gastric surgery still constitutes a diagnostic and therapeutic problem of importance. The situation and general characteristics and symptoms of recurrent peptic ulcer are described by Rivers and Gardner,¹⁷⁰ who present

168. Walters, W.: Cardial (Gastric) Ulcers: Results of Operation for Apparently Inaccessible Lesions, *Arch. Surg.* **41**:542 (Aug.) 1940.

169. Wangensteen, O. H.; Varco, R. L.; Hay, L.; Walpole, S., and Track, B.: Gastric Acidity Before and After Operative Procedure, with Special Reference to Role of Pylorus and Antrum: Preliminary Report of Clinical and Experimental Study, *Ann. Surg.* **112**:626, 1940.

170. Rivers, A. B., and Gardner, J. W.: Recurrent Peptic Ulcer, *J. A. M. A.* **115**:1779 (Nov. 23) 1940.

an excellent review of this particular phase of the ulcer problem. They point out what is not always clearly understood, that most recurrent ulcers occur in or near the vicinity of the stoma.

Primary jejunal ulceration is relatively uncommon. For this reason the report of a case by Zemp¹⁷¹ is worthy of mention, especially since there was an additional lesion of the jejunum which proved to be primary carcinoma. A further clinical and pathologic study of jejunal (anastomotic) ulcer is reported by Montgomery and Kirshbaum.¹⁷²

Small and Large Intestine.—Because of increased ability to diagnose the existence of lesions of the small bowel, many reports of these less common conditions are to be found in the literature. Congenital anomalies of the duodenum in infants and children are of importance because early recognition of their existence permits adequate surgical treatment. The occurrence of duodenal stenosis associated with nonrotation of the intestine, congenital duodenal valve formation, incomplete rotation of the duodenum, congenital obstruction of the duodenum and congenital duodenal atresia are noted by Saunders and Lindner,¹⁷³ Elman,¹⁷⁴ Potter¹⁷⁵ and Feggetter.¹⁷⁶ Diverticulum of the duodenum is a much more common condition and as a rule is asymptomatic. Weintraub and Tuggle¹⁷⁷ review the subject and report a series of 310 cases. It is of interest that in a fair proportion of these cases diaphragmatic hernia, presumably congenital,⁸³ occurred. The authors were unable to convince themselves that in any case were symptoms caused by pathologic changes in the diverticulum, and pathologic examination of the diverticulum in 17 autopsies and biopsies revealed only 1 instance of an inflammatory reaction. Ogilvie¹⁷⁸ agrees that clinical complications secondary to duodenal diverticulosis are rare but reports 4 instances in which definite complications arose secondary to congenital malformation. Obstruction of the duodenum, common bile duct or pancreatic

171. Zemp, F. E.: Primary Jejunal Ulcer, *South. M. J.* **33**:803, 1940.

172. Montgomery, M. M., and Kirshbaum, J. D.: Jejunal (Anastomotic) Ulcer: A Clinical and Pathologic Study with Report of Eight Cases Encountered in 13,000 Necropsies, *Arch. Int. Med.* **67**:609 (March) 1941.

173. Saunders, J. B. deC. M., and Lindner, H. H.: Congenital Anomalies of the Duodenum, *Ann. Surg.* **112**:321, 1940.

174. Elman, R.: Ladd's Operation for Cure of Incomplete Rotation and Volvulus of Small Intestine Producing Duodenal Obstruction in Infancy, *Ann. Surg.* **112**:234, 1940.

175. Potter, E. B.: Congenital Obstruction of Duodenum, *Northwest Med.* **39**:261, 1940.

176. Feggetter, S.: Congenital Duodenal Atresia, *Lancet* **2**:1881, 1940.

177. Weintraub, S., and Tuggle, A.: Duodenal Diverticula, *Radiology* **36**:297, 1941.

178. Ogilvie, R. F.: Duodenal Diverticula and Their Complications with Particular Reference to Acute Pancreatic Necrosis, *Brit. J. Surg.* **28**:362, 1941.

duct and true diverticulitis or perforation, with periduodenitis and cholangitis, were noted, and in 1 instance carcinoma was found in a diverticulum. Giant diverticulum of the small bowel, exclusive of the duodenum, is also rarely productive of symptoms. Duckett¹⁷⁹ reported 1 case of such a condition, in which eventually a resection of 42 cm. of ileum was necessary because of recurrent perforations.

Malignant lesions of the small bowel occur relatively infrequently as compared with similar lesions of the stomach and the large intestine. They occur with sufficient frequency, however, to warrant comment. In a review of cases of such lesions encountered at the Mayo Clinic Mayo¹⁸⁰ observes, as have most other physicians, that the jejunum was most frequently involved. The average age at which malignant disease of the small intestine was encountered was a little over 50 years, and it was much more frequently found among men than among women. An actual diagnosis of a malignant lesion of the small intestine was made in only 25 per cent of the cases, although undoubtedly the improvement in roentgenologic technic in recent years should definitely increase the percentage of preoperative diagnoses. Naturally, the symptoms calling attention to such lesions are recurrent attacks of partial intestinal obstruction, and general symptoms of anemia, weakness and fatigability. Annular adenocarcinoma is the most common lesion encountered, although sarcomas of various types are not infrequent. The percentage of cures following surgical intervention in this group of cases seems to be definitely higher than that following surgical intervention in cases of cancer of the stomach. Various authors¹⁸¹ report individual cases or small groups of cases of a malignant condition of the small bowel.

Intestinal obstruction due to extraluminal implants of endometrial tissue are also not rare. Much has been written about this subject, but an article by Aronsson¹⁸² is worthy of mention with reference to the clinical importance of the complications of endometriosis.

179. Duckett, J. W.: Giant Diverticulum or Duplication of the Intestine with Recurrent Perforations, *Ann. Surg.* **113**:528, 1941.

180. Mayo, C. W.: Malignancy of Small Intestine, *West. J. Surg.* **48**: 403, 1940.

181. Hunt, E. L., and Kaneb, G. D.: Primary Adenocarcinoma of the Jejunum, *New England J. Med.* **224**:353, 1941. Geyman, M. J.: Carcinoma of the Jejunum, *Radiology* **36**:468, 1941. Chont, L. K.: Sarcomas of the Small Intestine with Reference to Their Radiosensitivity, *ibid.* **36**:86, 1941. Mahaffey, H.: Report of Case of Fibrosarcoma of Ileum, *Kentucky M. J.* **38**:567, 1940. Frankman, C. F., and Drummond, D. H.: Primary Sarcoma of the Ileum with Perforation, *Ohio State M. J.* **36**:841, 1940. Gordon, W. C.: Primary Melanoma of the Small Intestine with Report of a Case, *Rev. Gastroenterol.* **8**:36, 1941. Willis, R. A.: Argentaffin Carcinomata ("Carcinoids") of Small Intestine, *M. J. Australia* **2**: 400, 1940.

182. Aronsson, A.: Case of Endometrial Implants in Small Intestine and in Navel, *Acta chir. Scandinav.* **84**:43, 1940.

Intussusception in the adult in the absence of tumor of the intestine is not particularly common, and for this reason the report of a case by Abrams¹⁸³ should be referred to. The diagnosis was established pre-operatively by roentgen examination, and surgical intervention was successful.

The diagnosis of acute intestinal obstruction should usually be reasonably obvious. At times, however, the diagnosis of this condition requires extreme skill, and valuable aid can be obtained from proper roentgen examination. Roentgenograms made without the use of a contrast medium usually demonstrate obstruction with distention of certain loops and the presence of fluid levels. Articles by Ascroft and Samuel¹⁸⁴ and by Ochsner¹⁸⁵ reaffirm the value of roentgenologic examination, although they agree that it is difficult, if not impossible, to gain precise information as to the exact level of obstruction. Also, differentiation of the various types of obstructive lesion is not to be expected in most instances. With rare exceptions, such an examination may be of particular diagnostic and therapeutic value in determining the absence of obstruction.

The use of the Miller-Abbott tube as an adjunct to roentgenologic diagnosis of intestinal obstruction is commented on by Ascroft and Samuel,¹⁸⁶ with particular reference to postoperative ileus, and by Golden and his collaborators.¹⁸⁷ This addition to the diagnostic armamentarium is of real value when employed conservatively by physicians skilled in its use. Inasmuch as intestinal intubation is also of therapeutic value, it is important that its advantages and the technic of its use, as well as the dangers that may accompany its employment, be thoroughly understood.

The physiologic disturbances occurring during acute intestinal obstruction are still worthy of further study. Fine and his collaborators¹⁸⁸ have previously reported on the reduction in volume of circulating plasma that is frequently encountered in this condition and that may be responsible for death. Their present communication is based on clinical evidence which confirms some of the previous experimental findings and

183. Abrams, H. S.: Intussusception: Particular Reference to Roentgen Diagnosis Without Opaque Media, *Radiology* **36**:490, 1941.

184. Ascroft, P. B., and Samuel, E.: The X-Ray Diagnosis of Acute Intestinal Obstruction, *Brit. J. Radiol.* **14**:11, 1941.

185. Ochsner, H. C.: Small Bowel Obstruction: A Roentgenologic Study, *Am. J. Digest. Dis.* **8**:16, 1941.

186. Ascroft, P. B., and Samuel, E.: Radiography in Postoperative Ileus, *Lancet* **2**:445, 1940.

187. Golden, R.; Leigh, O. C., and Swenson, P. C.: Roentgen-Ray Examination with the Miller-Abbott Tube, *Radiology* **35**:521, 1940.

188. Fine, J.; Hurwitz, A., and Mark, J.: A Clinical Study of the Plasma Volume in Acute Intestinal Obstruction, *Ann. Surg.* **112**:546, 1940.

indicates that distention of the small intestine, whether of functional or of mechanical origin, is associated with considerable loss in the volume of circulating plasma. As the plasma volume falls, there is a far greater rise in hematocrit values than can be explained by dehydration, however severe. The authors believe that dehydration and electrolyte imbalance are not responsible for the greater part of this loss of plasma, which they consider is generally proportional to the degree of gaseous distention of the bowel, since effective decompression of the small intestine restores the volume of plasma toward normal. This observation seems to be in contradistinction to that in cases of obstructive distention of the large bowel, in which no loss of plasma is to be demonstrated. It is to be pointed out that in their experimental work Fine and Gendel¹⁸⁹ have previously noted that the intravenous injection of physiologic solution of sodium chloride, or even of solution of acacia, is of little noticeable benefit. If prolonged vomiting has occurred, replacement of fluid and electrolytes is obviously indicated, but it is highly probable that the transfusion of plasma, together with deflation procedures, is of primary importance.

The indications for conservative or for radical measures in the treatment of intestinal obstruction, together with the various clinical considerations of this condition, are carefully reviewed by Schlicke and co-workers¹⁹⁰ and by Mayo and his collaborators.¹⁹¹ According to the latter, the importance of a correct choice of medical or surgical procedures is brought out by the statistical fact that the gross mortality rate for all cases of simple obstruction was approximately 22 per cent and that for cases of obstruction due to strangulation was about 24 per cent. In the face of these figures, it is obvious that a more exact understanding of the various features of intestinal obstruction is necessary. Schlicke and his colleagues stress the hazard of purgation and the barium sulfate meal in initiating attacks of acute obstruction. Indications for various therapeutic measures, medical and surgical, are carefully discussed by Wangenstein,¹⁹² whose article includes a detailed consideration of such measures as the use of solutions of sodium chloride, transfusion of whole blood and plasma, inhalation of high concentrations of oxygen and intestinal decompression. The value of roentgen examination fol-

189. Fine, J., and Gendel, S.: Plasma Transfusion in Experimental Intestinal Obstruction, *Ann. Surg.* **112**:976, 1940.

190. Schlicke, C. P.; Bargaen, J. A.; and Dixon, C. F.: The Management of Intestinal Obstruction, *J. A. M. A.* **115**:1411 (Oct. 26) 1940.

191. Mayo, C. W.; Miller, J. W., and Stalker, L. K.: Acute Intestinal Obstruction, *Surg., Gynec. & Obst.* **71**:589, 1940.

192. Wangenstein, O. H.: Value of Diagnostic Criteria for Choice of Therapeutic Procedure in Management of Acute Intestinal Obstruction: Experimental and Clinical Observation, *Radiology* **35**:680, 1940.

lowing decompression therapy is emphasized, and careful attention is directed to the indications for surgical intervention. The maintenance of fluid and nutritional requirements by the use of intestinal intubation in cases of obstruction is thoroughly discussed by Abbott,¹⁹³ who points out that the details of such therapy differ, depending on the level of obstruction. In the presence of high obstruction in the alimentary canal the tube may be placed by surgical means in such a position that food is introduced below the obstructing lesion. Under such conditions, the character of the food must be carefully planned to avoid undue irritation from too little or from too much digestion. In the presence of low intestinal obstruction the tube may be passed to the level of the obstruction itself and then used to recover the residue of food eaten normally, once deflation has been accomplished. Under these circumstances, one must supply those foods most needed by the patient and at the same time avoid all foods the residue of which cannot be drawn back through the tube. A timely note of caution as to the use of decompression by means of a tube is presented by Wakefield and Friedell¹⁹⁴ in a paper on the structural significance of the ileocecal valve. These authors point out that varying degrees of developmental incompetence of the valve exist. In cases of obstruction of the colon intestinal suction should be used cautiously. The relief obtained by decompression of the small bowel in cases of colonic obstruction must not be allowed to mask a dangerously obstructed cecum. They insist that surgical intervention is indicated when medical measures fail to decompress the obstructed area. By inference, one may reemphasize the importance of repeated roentgen examination of the abdomen in order to determine the results of decompression therapy.

The possibility of Meckel's diverticulum as a cause of symptoms in the adult is still not too commonly considered. For this reason, Noel's¹⁹⁵ report of 25 cases is of interest, inasmuch as in 17 of them the abnormality occurred in persons between the ages of 20 and 50 years. Symptoms of obstruction or of an acute inflammatory process were the rule. Intestinal bleeding was present on several occasions, however, a symptom which should always necessitate consideration of this condition as an underlying cause if no other evidence of disease is to be obtained. Everhart¹⁹⁶ points out that in children failure to suspect a Meckel diverticulum as an explanation for vague abdominal pain associated with

193. Abbott, W. O.: Fluid and Nutritional Maintenances by the Use of an Intestinal Tube, *Ann. Surg.* **112**:584, 1940.

194. Wakefield, E. G., and Friedell, M. T.: The Structural Significance of the Ileocecal Valve, *J. A. M. A.* **116**:1889 (April 26) 1941.

195. Noel, W. W.: Meckel's Diverticulum, *Am. J. Surg.* **49**:454, 1940.

196. Everhart, M. W.: Complications of Meckel's Diverticulum in Infancy and Childhood with Analysis of Fourteen Cases, *J. Pediat.* **17**:483, 1940.

a history of the passage of blood by rectum may result in a high mortality. He reports 8 deaths in 14 cases and indicates that this high mortality was related to temporizing measures that had been employed in the absence of a specific diagnosis.

Two papers by Eggers¹⁹⁷ and Arnheim¹⁹⁸ on diverticulitis of the colon are worthy of comment. Both authors pay particular attention to the surgical complications of this condition, and unless the papers are carefully read, one gets the impression that surgical intervention is frequently indicated for diverticulitis of the sigmoid flexure of the colon. Two thirds of Eggers' patients received satisfactory relief from conservative treatment, but the author warns that lack of adequate measures may lead to the occurrence of surgical complications, the risk of which is great. Arnheim lists in detail the following complications, which he considers to be associated with this condition: peritonitis resulting from passage of organisms through an inflamed diverticulum without perforation; perforation of an inflamed diverticulum; formation of a fistula; peridiverticulitis; metastatic suppuration, and carcinoma arising from a diverticulum. Judging from my experience and from that of many others, it seems that somewhat too much emphasis is laid on these complications, although most of them can and do occasionally occur. The danger of carcinoma secondary to diverticulitis is probably negligible, for statistics show that the incidence of a malignant process in persons with this condition is no greater than in the general population. Metastatic suppuration is an extremely serious complication which rarely occurs. The striking fact is that, as a rule, perforation and abscess formation are not common, although the diagnosis of such a condition should always be considered in older people in the presence of acute abdominal symptoms with associated fever and leukocytosis. The frequency with which peritonitis occurs without evidence of perforation is problematic. Perusal of these two articles is of value, but it seems to me that in the vast majority of instances correct diagnosis and intensive but conservative medical measures will provide an effective means of control.

The question of colonic cancer is inextricably associated with that of polyposis. The potential danger of adenomatous polyps is generally recognized, but an occasional case that has been followed over some time is worth reporting for emphasis. Jackman¹⁹⁹ tells of a patient aged 58 whose first examination led to the discovery of two small sigmoid polyps. Fulguration was advised and refused, and the patient was not seen again

197. Eggers, C.: Acute Diverticulitis and Sigmoiditis, *Ann. Surg.* **113**:15, 1941.

198. Arnheim, E. E.: Diverticulitis of Colon, with Special Reference to Surgical Complications, *Ann. Surg.* **112**:352, 1940.

199. Jackman, R. J.: The Relationship of Polyps of the Colon to Carcinoma, *Proc. Staff Meet., Mayo Clin.* **16**:11, 1941.

for five years. At this time he returned to the clinic, where proctoscopic examination revealed adenocarcinoma. Such an experience, unfortunately, is not rare and proves the dangers inherent in too conservative treatment of an apparently benign lesion. The difficulty with which polyps of the rectum and the lower part of the sigmoid may be demonstrated by roentgen examination is pointed out by Green.²⁰⁰ There can be little doubt that symptoms suggesting a disturbance in the rectum and the rectosigmoid are properly studied by digital and sigmoidoscopic examination, and the point made by the author is sound.

An excellent description of the pathologic variations found in polypoid growths of the large bowel, with particular reference to malignant changes, is presented by David.²⁰¹ He discusses the histologic aspects of benign adenoma, villous polyp of the hereditary type seen in multiple polyposis, so-called lymphoid polyp, which is really a form of lymphoid hyperplasia, and pseudopolyp of an inflammatory type. He also points out the unfortunate fact that specimens for biopsy removed locally through a sigmoidoscope do not always present the entire picture, inasmuch as they may not include malignant lesions, even though the latter are present. The paper is worthy of study, since it includes a report of 200 resected cancers and 100 specimens of supposedly benign polyps of the colon and rectum.

The occurrence of multiple primary malignant lesions of the large intestine is recorded by Schweiger and Bargaen,²⁰² who divide such lesions into two groups: those in which multiple cancers occur simultaneously, and those in which they occur at different times. The distribution and development of the malignant lesions in the cases reported by the authors are somewhat out of the ordinary and are, therefore, of real interest. Surgical treatment, of course, is the only method of choice. A statistical analysis of the distribution of malignant growths in the colon and the associated symptoms is presented by Buirge.²⁰³ Two points are worthy of mention, namely, that bleeding did not occur in slightly under 10 per cent of the entire series of cases in which autopsies were recorded and that hemorrhoids were associated in a similar percentage. These points need constant emphasis, since only too frequently bleeding is attributed to easily demonstrable hemorrhoids and no further search is made for lesions of a more serious nature.

200. Green, W. W.: Polyps of the Lower Sigmoid and Rectum, *Ohio State M. J.* **37**:38, 1941.

201. David, V. C.: Some Etiologic and Pathologic Factors in Cancer of Large Bowel, *Arch. Surg.* **41**:257 (Aug.) 1940.

202. Schweiger, L. R., and Bargaen, J. A.: Multiple Primary Malignant Lesions of the Large Bowel, *Arch. Int. Med.* **66**:1331 (Dec.) 1940.

203. Buirge, R. E.: Carcinoma of the Large Intestine: Review of Four Hundred and Sixteen Autopsy Records, *Arch. Surg.* **42**:801 (May) 1941.

Mayo and Lovelace²⁰⁴ report a thorough statistical study on malignant lesions of the cecum and the ascending colon. In 885 cases in which surgical treatment was employed the lesions were distributed between the cecum and the ascending colon, including the hepatic flexure; they constituted 30 per cent of all malignant lesions of the abdominal portion of the colon and only 12 per cent of the malignant lesions of the entire colon, including the rectosigmoid, the rectum and the anal canal. As in most reports, the association of serious anemia with cancer of the right side of the colon is stressed. According to the authors lymphatic involvement need not indicate a hopeless prognosis, inasmuch as in nearly 50 per cent of the cases in which resection revealed such metastases the patients were alive five years or more after operation and in only 57 per cent of all cases was the period of survival five years. In 25 per cent of cases in which resection was done the patients lived for twenty years after the operation.

Several reports concern the results of the surgical treatment of cancer of the rectum. Dukes²⁰⁵ studied variations in the histologic structure of rectal cancer and its tendency to metastasize in 1,000 cases in which treatment was by radical excision. According to him, the disease is about twice as common in men as in women. He comments on the not infrequent occurrence of the disease in younger persons and notes the greater incidence of lymphatic metastasis in this age group. He particularly emphasizes the importance of the microscopic structure of rectal cancer since knowledge of this may allow an estimate of the rate of growth and may even indicate the extent of local lymphatic or venous spread. Shedden,²⁰⁶ also, reviews the subject of rectal and sigmoid cancer and stresses the importance of Dukes's method of grading the malignant forms. He notes that metastasis to the lymph nodes is not always a late phenomenon and that a specimen taken for biopsy may not indicate the true pathologic grade of the tumor. Digital, sigmoidoscopic and roentgen examinations, with appropriate treatment, are important, since 93 per cent of patients with grade A cancers—or of the type confined to the rectal walls—survive five years whereas of those patients with involvement of the lymph nodes only 23 per cent have a similar survival period. Shedden advocates the Miles operation as the treatment of choice and expresses the feeling that cure may well be obtained in over 50 per cent of patients. Broders, Buie and

204. Mayo, C. W., and Lovelace, W. R. II.: Malignant Lesions of the Cecum and Ascending Colon, *Surg., Gynec. & Obst.* **72**:698, 1941.

205. Dukes, C. E.: Cancer of the Rectum: Analysis of One Thousand Cases, *J. Path. & Bact.* **50**:527, 1940.

206. Shedden, W. M.: Cancer of Rectum and Sigmoid, *New England J. Med.* **223**:801, 1940.

Laird²⁰⁷ consider statistically the importance of careful grading of rectal cancers. After comparing Broders' method of grading with that of Dukes, the authors conclude that a combination of the two classifications yields a prognosis of survival which is more accurate than that obtained by either method alone. Coller and his collaborators,²⁰⁸ in a study somewhat similar to the one just mentioned, report that in the spread of carcinoma along any zone of diffusion the nodes are not necessarily involved in continuity but may be involved at some distance, with normal nodes intervening between the primary site and the metastases.

A rather unusual case is presented by Hval and Schnitler.²⁰⁹ They describe inflammatory-like strictures in the intestinal tract which simulate malignant disease. The size varies from that of a man's head to that of a walnut and the consistency from firm or ligneous to soft, tumors of the last-named type being due to abscess formation. Occasionally such tumors are reported as occurring in the colon and rectum.

To those interested in developmental defects, Gray's²¹⁰ report of a case of triplication of the large intestine will be worth reading. A much more common type of congenital abnormality is megacolon, of which an unusual example is cited by Ford.²¹¹ The condition was recognized in an infant aged 7 months; by the time the child was 7 years old the colon was dilated so tremendously that the ileocecal junction was in the precordial region and the diaphragm was at the level of the nipples. An instance of still larger megacolon was noted by Bach and collaborators²¹² in a mentally deficient patient aged 27. At necropsy the circumference of the colon was 82.4 cm., probably one of the largest to be reported. In this case it is not clear that the condition was congenital. The medical treatment of megacolon is reviewed and outlined in detail by Law,²¹³ who contributes nothing new but

207. Broders, A. C.; Buie, L. A., and Laird, D. R.: Prognosis in Carcinoma of the Rectum, *J. A. M. A.* **115**:1066 (Sept. 28) 1940.

208. Coller, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastasis of Carcinoma of the Rectum, *Surgery* **8**:294, 1940.

209. Hval, E., and Schnitler, K.: Inflammation-Like Strictures in Intestinal Tract with Clinical Picture of Malignant Tumors, *Nord. med. (Med. rev., Bergen)* **8**:1968, 1940.

210. Gray, A. W.: Triplication of the Large Intestine, *Arch. Path.* **30**:1215 (Dec.) 1940.

211. Ford, S. A.: Congenital Megacolon Observation, *West Virginia M. J.* **36**:317, 1940.

212. Bach, A. C.; Imerman, H. M., and Kearns, J. J.: Giant Colon in an Adult Psychotic Patient with Necropsy Report, *Am. J. Digest. Dis.* **7**:523, 1940.

213. Law, J. L.: Treatment of Megacolon with Acetylbetamethylcholine Bromide, *Am. J. Dis. Child.* **60**:262 (Aug.) 1940.

reports the successful treatment of 15 patients. Medical management was accompanied by complete evacuation of the colon by the use of enemas, liquid petrolatum and acetylbetamethylcholine bromide. Once the colon was practically emptied, the patient was put on a regimen of which the most important measure was the administration of acetylbetamethylcholine bromide twice a day in gradually increasing doses just short of toxicity. Certainly in children such a maneuver seems entirely warranted before resort to sympathectomy.

The unusual condition of gas cysts of the intestine is reviewed by Jackson,²¹⁴ who reports a case. This curious condition seems to be associated with the introduction of gas through the lymphatic vessels at the site of an ulcer or a break in the mucosa of the stomach or the bowel, with subsequent distribution along the lymphatic vessels to points between the layers of the intestinal walls in the form of cystic dilatations. The condition is self limited and therefore requires no operative treatment when it is recognized.

The only contribution of any interest in relation to the problem of ileitis is a report by Stewart and Jones²¹⁵ on the pathoanatomic aspects of chronic ulcerative cecitis, a spontaneous disease of the rat. The condition is slowly progressive and resulted in extensive involvement of the cecum and the adjacent lymph nodes. Advanced lesions have been found in old rats, surviving for months, although emaciated and presenting large palpable abdominal masses. The condition is quite different from other diseases known to occur spontaneously in the rat and is a possible basis for comparison with human ileitis, which it resembles in many respects.

Appendicitis.—Of anatomic interest is an article by De Garis²¹⁶ on the topography and development of the cecum-appendix. He describes the developmental sequence of growth of the cecum and the appendix and states that variations in growth render the definition of McBurney's point futile. Because of the highly variable topography of the junction between the appendix and the cecum, it is obvious that in many instances the appendix may be found at some distance from its expected position. Waugh's²¹⁷ report of 15 cases of appendix vermiformis duplex is of anatomic and embryologic interest. Other rare condi-

214. Jackson, J. A.: Gas Cysts of the Intestine, Surg., Gynec. & Obst. **71**:675, 1940.

215. Stewart, H. L., and Jones, B. F.: Pathologic Anatomy of Chronic Ulcerative Cecitis: A Spontaneous Disease of the Rat, Arch. Path. **31**:37 (Jan.) 1941.

216. De Garis, C. F.: Topography and Development of the Cecum-Appendix, Ann. Surg. **113**:540, 1941.

217. Waugh, T. R.: Appendix Vermiformis Duplex, Arch. Surg. **42**:311 (Feb.) 1941.

tions involving the appendix, such as primary adenocarcinoma, carcinoid tumor, benign and malignant cystic tumors and calcified mucocele, are mentioned in articles by Schuldt,²¹⁸ Woodruff and McDonald²¹⁹ and Ostrum and Miller.²²⁰

Experiments directed toward the production of appendicitis in animals are reported by Buirge and his associates.²²¹ Apparently by artificial obstruction of the appendix it was possible to produce acute inflammatory, obstructive, gangrenous and ruptured parietal appendicitis in the rabbit, in the chimpanzee and in man. Early appendicular obstruction was attended by minimal histologic inflammatory changes, and the release of the appendical obstruction resulted in prompt repair of the injured tissues. In man, the histologic picture of diffuse appendicitis was reproduced by induced obstruction in the exteriorized vermiform appendix. Luminal obstruction in an appendix with active secretory function would appear to be the dominant factor in provoking appendicitis.

The "initial perfusion resistance pressure" was determined for 43 appendixes removed at operation by Koster and Shapiro.²²² These authors came to conclusions somewhat similar to those of Buirge and co-workers, but they feel that while secretion against obstruction may be a factor in the pathogenesis of acute appendicitis, it is not the only mechanism.

Various clinical conditions may simulate acute appendicitis or render such a diagnosis extremely difficult. Complete situs inversus obviously complicates the diagnostic possibilities, and a case in point is that cited by Lawrence.²²³ The appearance of a foreign body (common pin) in the vermiform appendix is reported by Ehrlich.²²⁴ Oxyuriasis has long been suspected of causing appendical symptoms, probably by obstruction of the lumen by the walls. Reports by Carlisle and

218. Schuldt, F. C.: Primary Adenocarcinoma of the Appendix and Carcinoid Tumors, *Minnesota Med.* **23**:791, 1940.

219. Woodruff, R., and McDonald, J. R.: Benign and Malignant Cystic Tumors of Appendix, *Surg., Gynec. & Obst.* **71**:750, 1940.

220. Ostrum, H. W., and Miller, R. F.: Calcified Mucocele of the Appendix with Rupture, *Radiology* **36**:356, 1941.

221. Buirge, R. E.; Dennis, C.; Varco, R. L., and Wangenstein, O. H.: Histology of Experimental Appendical Obstruction (Rabbit, Ape and Man), *Arch. Path.* **30**:481 (Aug.) 1940.

222. Koster, H., and Shapiro, A.: Role of Intraluminal Obstruction in the Pathogenesis of Acute Appendicitis, *Arch. Surg.* **41**:1251 (Nov.) 1940.

223. Lawrence, C. W.: Appendicitis with Complete Situs Inversus Viscerum, *J. Kansas M. Soc.* **41**:333, 1940.

224. Ehrlich, M. C.: Foreign Bodies in the Vermiform Appendix with Report of Case, *Illinois M. J.* **78**:268, 1940.

Carrel²²⁵ and Kaplan²²⁶ deal with this possibility. Mesenteric adenitis has long been considered capable of causing attacks similar to those of acute appendicitis and may occur in relation to various acute infections, including the so-called rheumatic infections and infections of the upper respiratory tract, as well as in association with tuberculous adenitis. Reports by Urech²²⁷ and Wilensky²²⁸ illustrate such a possibility. Another rather unusual condition capable of mimicking attacks of acute appendicitis is perforation of the small intestine by swallowed foreign bodies. Melville²²⁹ records 6 instances, in each one of which the clinical features were comparable to those noted in acute appendicitis. Traumatic appendicitis has been frequently commented on by various authors and is still a controversial subject. However, the consensus seems to be that a relation exists between trauma and acute appendicitis in certain cases. Seven cases of acute appendicitis following severe trauma to the abdomen are reported by Rhodes and Birnbaum.²³⁰

Reports of large groups of cases of acute appendicitis reveal certain important clinical points. King²³¹ reported a mortality rate as low as 0.34 per cent for acute, uncomplicated appendicitis, and in a paper by Stafford and Sprong²³² no deaths were reported in 838 cases in which perforation had not occurred. Rumbold²³³ records a death rate of 0.5 per cent in 199 cases of acute appendicitis. Figures presented by Bower²³⁴ indicate that in Pennsylvania, where a statewide educational campaign has been in progress since 1933, the fatalities from this condition are gradually decreasing. The vast majority of deaths from appendicitis in all instances are undoubtedly due to associated peritonitis secondary to delay and perforation, and a rather

225. Carlisle, J. B., and Carrel, R. M.: Oxyuriasis and Appendicitis, *J. Missouri M. A.* **37**:386, 1940.

226. Kaplan, J. H.: Oxyuriasis as an Etiological Factor of Appendicitis, *Illinois M. J.* **78**:441, 1940.

227. Urech, E.: Mesenteric Adenitis Simulating Appendicitis, *Schweiz. med. Wchnschr.* **70**:1152, 1940.

228. Wilensky, A. O.: General Abdominal Lymphadenopathy with Special Reference to Nonspecific Mesenteric Adenitis, *Arch. Surg.* **42**:71 (Jan.) 1941.

229. Melville, C. B.: Perforation of Small Intestine by Swallowed Foreign Bodies, *Australian & New Zealand J. Surg.* **10**:146, 1940.

230. Rhodes, G. K., and Birnbaum, W. D.: Traumatic Appendicitis, *California & West. Med.* **53**:162, 1940.

231. King, H. J.: Problem of Acute Appendicitis, *Am. J. Surg.* **49**:104, 1940.

232. Stafford, E. S., and Sprong, D. H., Jr.: The Mortality from Acute Appendicitis in the Johns Hopkins Hospital, *J. A. M. A.* **115**:1242 (Oct. 12) 1940.

233. Rumbold, L.: Some Factors in a Lowered Mortality Rate for Acute Appendicitis: Analysis of 2,013 Consecutive Cases, *Arch. Surg.* **42**:25 (Jan.) 1941.

234. Bower, J. O.: Clinical and Surgical Aspects of Spreading Peritonitis Complicating Acute Perforative Appendicitis, *Minnesota Med.* **23**:755, 1940.

discouraging note is sounded by Boyce,²³⁵ who states that during a nine year period the annual mortality rate in a series of 4,207 cases of acute appendicitis has remained practically stationary. Like all other authors, he stresses the necessity of educating the public as regards prompt operation and abstinence from purgation in the presence of abdominal pain. A higher percentage of favorable results seems to have been obtained in New York state. Nassau and his colleagues²³⁶ report that in a series of 4,650 cases of all forms of appendicitis the mortality rate was 3.3 per cent and in a series of 3,451 cases of acute appendicitis it was 4.2 per cent. Thompson and his colleagues²³⁷ give a total mortality rate of 2.7 per cent in 741 cases of appendicitis and state that a dramatic reduction in the mortality rate has been obtained by the use of sulfanilamide. McCreery and Serrell,²³⁸ in an excellent report of the treatment of acute appendicitis in the suburbs of New York, record a mortality rate of 1.3 per cent in a series of 525 cases and also express the belief that the use of sulfanilamide in the presence of peritoneal involvement is an important therapeutic measure. Schmidt,²³⁹ also, calls attention to the advantages of this newer form of treatment.

Boyce²⁴⁰ bases his conclusions on 421 cases of acute appendicitis in persons over 39 years of age, 738 cases in children under 12 years and over 3,000 cases in persons between the ages of 13 and 39 years. He comments in detail on the difficulties of diagnosis in the older age group, in which symptoms develop slowly and physical findings are atypical. The mildness of the initial pain, which is often only discomfort, the variable localization of tenderness and the frequent absence of an elevated temperature, pulse rate or marked leukocytosis all render the diagnosis difficult and tend to delay a correct decision as to operative intervention. These facts are reasonably well known but cannot be reviewed too frequently.

235. Boyce, F. F.: The Mortality of Acute Appendicitis: A Continuing Study (4,207 Cases) from the Charity Hospital of Louisiana at New Orleans, New Orleans M. & S. J. **93**:300, 1940.

236. Nassau, C. F.; Lorry, R. W., and Pulaski, E. J.: Treatment of Appendicitis at Frankford Hospital: A Thirty-Six Year Survey of 4,650 Cases, Arch. Surg. **42**:296 (Feb.) 1941.

237. Thompson, J. E.; Brabson, J. A., and Walker J. M.: The Intra-Abdominal Application of Sulfanilamide in Acute Appendicitis, Surg., Gynec. & Obst. **72**:722, 1941.

238. McCreery, J. A., and Serrell, H. P.: Acute Appendicitis in a Suburban Community, Surgery **9**:349, 1941.

239. Schmidt, E. R.: Peritonitis and Appendicitis, J. A. M. A. **115**:1360 (Oct. 19) 1940.

240. Boyce, F. F.: Acute Appendicitis in Middle and Later Life: An Analysis of Four Hundred and Twenty-One Cases in Individuals Over Thirty-Nine Years of Age, Am. J. Digest. Dis. **8**:223, 1941.

Ward ²⁴¹ suggests that further reduction in fatalities may be obtained by augmenting chemotherapy with the intelligent use of gastrointestinal decompression and cites rather convincing figures. The complication of mesenteric thrombosis is not too generally recognized, and for this reason Rosenqvist's ²⁴² excellent clinical description of the condition is worthy of notice. Acute hepatitis, jaundice and abnormal bleeding, more uncommon complications of acute appendicitis, are reported by Simeone and Stewart,²⁴³ with illustrative cases. Prothrombin deficiency was an important complicating factor. A curious complication which occasionally follows acute perforated appendicitis is the formation of a false diverticulum, with subsequent acute inflammation and perforation. Kline and his colleagues ²⁴⁴ report a fairly large group of cases of this condition, which may explain some of the acute emergencies occurring after appendectomy. Another fortunately uncommon condition is vesico-appendical fistula, a number of instances of which are reported by Pemberton, Pool and Miller.²⁴⁵ The treatment of choice is appendectomy, with simple closure of the opening in the bladder.

Rather encouragingly Estrada and Meñez ²⁴⁶ conclude, on the basis of histologic studies of a large number of so-called chronic appendixes, that confirmatory pathologic changes are absent in a great percentage of cases in which the clinical diagnosis is chronic appendicitis.

Finally, it may be proper to refer to three articles on one other condition that occasionally simulates appendicitis and results in an acute abdominal emergency, namely, primary torsion and infarction of the appendixes epiploicae. Nine cases of this condition are reported by Pines and co-workers,²⁴⁷ LeVay ²⁴⁸ and Upham and McGrattan.²⁴⁹

241. Ward, R.: Appendicitis with Complications: Reduction in Mortality Due to Use of Continuous Gastrointestinal Decompression, *West. J. Surg.* **48**:469, 1940.

242. Rosenqvist, H.: Mesenterial Pyemia in Connection with Appendicitis, *Nord. med. (Hygiea)* **8**:2159, 1940.

243. Simeone, F. A., and Stewart, J. D.: Acute Hepatitis, Jaundice and Abnormal Bleeding as Complications of Acute Appendicitis with Perforation, *New England J. Med.* **223**:632, 1940.

244. Kline, B. S.; Young, A. M., and Straus, R.: False Diverticulum Formation Following Acute Perforative Appendicitis, *Arch. Path.* **31**:25 (Jan.) 1941.

245. Pemberton, J. de J.; Pool, T. L., and Miller, J. M.: Vesico-Appendiceal Fistulas, *J. Urol.* **44**:274, 1940.

246. Estrada, J. R., and Meñez, S. C.: Chronic Appendicitis: A Study of Its Clinical and Pathological Diagnosis, *Philippine M. A. J.* **20**:505, 1940.

247. Pines, B.; Rabinovitch, J., and Biller, S. B.: Primary Torsion and Infarction of the Appendixes Epiploicae, *Arch. Surg.* **42**:775 (April) 1941.

248. LeVay, A. D.: Torsion and Inflammation of the Appendixes Epiploicae, *Lancet* **1**:141, 1941.

249. Upham, R., and McGrattan, V.: Torsion of Appendixes Epiploicae: Review of the Literature and Report of One Case, *New York M. Coll. & Flower Hosp. Bull.* **3**:240, 1940.

Infectious and Parasitic Diseases.—A wealth of reports from all over the world concerning infectious and parasitic diseases of the gastrointestinal tract reflect a welcome increase in interest in this important phase of disease. Relatively few additions have been made to our knowledge of this subject, but I believe it is important to emphasize this growing interest, particularly because of the accumulating evidence that various forms of chemotherapy are effective in shortening the course of many of these acute infections or in bringing about a cure once the cause of the condition has been determined. From the point of view both of public health and of the relief of the individual patient, the renewed investigation of specific infections of the alimentary canal is to be desired. Too much emphasis cannot be laid on the employment of relatively simple laboratory procedures that will aid in the identification of the underlying cause of symptoms, especially since adequate facilities already exist in many states in the form of public health or hospital laboratories.

Epidemics of acute gastrointestinal upsets apparently associated with contact or droplet infection are numerous, and the description of one such epidemic by Dack²⁵⁰ illustrates the usual course of such illnesses. In spite of careful laboratory studies, the etiologic relations of this particular group were not determined, but indications for further studies are to be found.

An extremely careful pathologic study of an epidemic of diarrhea in the newborn is presented by Lyon and Folsom.²⁵¹ The epidemic described was the third encountered in the nursery of a general hospital during the last sixteen years. The authors, after careful study, believe that the diarrhea noted in these three epidemics differs from bacillary dysentery of the newborn. Postmortem examinations revealed catarrhal and hemorrhagic involvement of the intestinal tract, with moderate enlargement of the mesenteric glands, and associated edema of the brain, with pinpoint hemorrhages throughout the brain and the central nervous system. It was impossible to isolate any of the forms of dysentery bacilli, and the course of the disease seemed to be primarily that of intracranial involvement followed by diarrhea. On the basis of two clinical observations, it is suggested that the malady was an expression of infection with influenza virus. Citrated blood from a patient recently convalescent from influenza seemed to be beneficial for 3 of the most severely ill infants, and a mother apparently infected by her own ill infant responded to the infection with the symptoms of clinical influenza.

250. Dack, G. M.: An Epidemic of Acute Digestive Upsets of Unknown Etiology, *Am. J. Digest. Dis.* 8:210, 1941.

251. Lyon, G. M., and Folsom, T. G.: Epidemic Diarrhea of Newborn: I. Clinico-Epidemic, Pathologic and Therapeutic Aspects, *Am. J. Dis. Child.* 61:427 (March) 1941.

Greenberg, Frant and Shapiro²⁵² report an interesting case of bacillary dysentery caused by organisms of the Flexner type V in a newborn infant who acquired the disease apparently two and a half days after contact with its mother, who had already had the condition for five days. It is possible that in the newborn immunity to such infection is relatively low.

The source of bacillary dysentery can frequently be traced to food handlers. Quinlivan²⁵³ records an outbreak of 105 cases of this disease in a boys' camp of 340 persons. Dysentery bacilli of the Flexner group were obtained from those who were sick with the disease and eventually also from fecal specimens from employees of the dairy which was the source of the milk supply of the camp.

Because of recent interest in the Newcastle bacillus, isolated occasionally in cases of dysentery in Great Britain, Rhodes²⁵⁴ studied the prevalence of bacillary dysentery in Edinburgh. In 1940, 187 cases were identified, in 113 of which the disease was due to the Flexner bacillus, in 47 to the Newcastle bacillus and in 27 the Sonne bacillus. The introduction of dysentery in epidemic form is illustrated by the report of Fleitas,²⁵⁵ who describes the most recent epidemic in the Chaco, in Paraguay. Apparently, an epidemic began among Bolivian troops, and the disease was transmitted to Paraguayan troops and by them to the civilian population. Dysentery bacilli, especially of the Shiga type, were found in cases of acute, as well as chronic, dysentery and *Salmonella* and *Eberthella* were also found. Branston and Eldering,²⁵⁶ of the Western Michigan Division of the Bureau of Laboratories of the Michigan Department of Health, made a careful study of dysentery in the lower peninsula of that state and isolated dysentery bacilli in connection with the examination of nearly 2,600 specimens of feces and urine. The Sonne type of dysentery bacillus predominated, 56 cultures of this organism being obtained as compared with 24 of the Flexner group. In addition, there were 31 cultures positive for *Bacillus alkalescens* and 12 cultures of incompletely identified bacilli of the dysentery group.

A point of importance in regard to the clinical picture of Sonne dysentery is made by Cooke,²⁵⁷ who reports 2 cases of children who died

252. Greenberg, M.; Frant, S., and Shapiro, R.: Bacillary Dysentery Acquired at Birth, *J. Pediat.* **17**:363, 1940.

253. Quinlivan, J. J.: Milk-Borne Bacillary Dysentery, *New York State J. Med.* **40**:1027, 1940.

254. Rhodes, A. J.: Dysentery Due to *B. Dysenteriae* Newcastle: Prevalence in Edinburgh, *Lancet* **1**:244, 1941.

255. Dysentery in Paraguay, *Foreign Letters, J. A. M. A.* **116**:1594 (April 5) 1941.

256. Branston, M., and Eldering, G.: Cultures of the Dysentery Group Isolated in Western Michigan, *J. Infect. Dis.* **68**:113, 1941.

257. Cooke, R. T.: Fulminating Sonn  Dysentery, *Brit. M. J.* **2**:151, 1940.

of this condition in less than twenty-four hours. In neither case was there diarrhea. Further observations by Cruickshank and Swyer²⁵⁸ on a dysentery due to the Sonne bacillus contain important data on the clinical and bacteriologic aspects. These authors describe an outbreak of dysentery among infants and young children, with a total of 32 reported cases. Again, the intestinal symptoms were not severe. Particular interest was directed toward associated symptoms of the respiratory tract. Rhinitis was present in 10 cases, bronchitis in 5 and otitis media in 3. The authors suggest that gastroenteritis of the dysentery type seems, in some degree, to be a predisposing factor to secondary infections of the upper respiratory tract. An important diagnostic point lies in their statement that by the use of rectal swabs, rather than fecal specimens, a much higher proportion of positive cultures can be obtained. The persistence of the Sonne bacillus in the intestinal tract after the subsidence of the acute infection reveals the importance of the convalescent carrier as a reservoir for the spread of the infection, a fact which has been observed by others. The possible importance of *B. alkalescens* as a cause of dysentery is discussed by Felsen and Wolarsky,²⁵⁹ although actual proof that this organism acts as a pathogen is still to be obtained.

The value of chemotherapy in treating bacillary dysentery and other infections due to the colon-typhoid-dysentery group of organisms is still on trial, but undoubtedly sulfanilamide or one of its derivatives may be of prime importance in treating the acute forms of bacillary dysentery. One of the best reports to date on the use of sulfanilylguanidine (sulfaguanidine) is that by Lyon.²⁶⁰ By treating alternate patients with severe or relatively severe bacillary dysentery with this drug he observed 23 treated subjects and a similar number of untreated controls. Because of the wide variations in the clinical manifestations of the disease, the results are not conclusive, but there seems a reasonable basis for the author's conclusion that sulfanilylguanidine is effective in the treatment of acute bacillary dysentery, especially if it is administered within the first three or four days of the illness. The choice of this particular drug may be important, inasmuch as it has been shown by Marshall and his collaborators²⁶¹ to be absorbed relatively poorly from the gastrointestinal

258. Cruickshank, R., and Swyer, R.: Outbreak of Sonn  Dysentery, *Lancet* 2:803, 1940.

259. Felsen, J., and Wolarsky, W.: Bacillary Dysentery Due to *Bacillus Alkalescens*, *New York State J. Med.* 40:1303, 1940.

260. Lyon, G. M.: Chemotherapy in Acute Bacillary Dysentery: II. Clinical Use of Sulfanilylguanidine, *West Virginia M. J.* 37:54, 1941.

261. Marshall, E. K., Jr.; Bratton, A. C.; White, H. J., and Litchfield, J. T., Jr.: Sulfanilylguanidine: Chemotherapeutic Agent for Intestinal Infections, *Bull. Johns Hopkins Hosp.* 67:163, 1940.

tract and therefore to permit a relatively high concentration in the intestine, without unduly raising the level in the blood. Whether the drug possesses real clinical advantages over other preparations, such as sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) remains to be seen. Marshall, Bratton, Edwards, and Walker,²⁶² who were among the first to investigate sulfanilylguanidine experimentally, to a great extent confirm for a somewhat smaller group the clinical observations reported by Lyon. The results were not uniformly good unless treatment was initiated before the third day of the disease; after this period the drug appeared to have little influence. Bacteriologic studies of the stools revealed, however, that in all 17 children treated the stools became free of dysentery organisms during therapy and remained negative during hospitalization. One child had a culture inconstantly positive for the Sonne type of bacillus during and after the administration of the drug. No toxic effects were observed.

That sulfathiazole may be equally effective, at least in some of the colon-typhoid-dysentery infections, is suggested by *in vitro* experiments of Libby and Joyner,²⁶³ who conclude that this drug is considerably more active against laboratory strains of known history and virulence than is sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) or sulfanilamide. Two reports are available on the effect of sulfapyridine therapy in the treatment of small groups of children with infectious diarrhea. Villani²⁶⁴ states that in all but 1 of 16 infants and children a rather violent type of infectious diarrhea was adequately controlled by various measures, including the use of sulfapyridine, results being obtained twenty-four to forty-eight hours after the first administration of the drug. There was a single death; 1 infant was unable to retain the drug, and chemotherapy was therefore discontinued. Welch and his collaborators²⁶⁵ also report successful treatment with this drug in 13 cases of acute bacillary dysentery and record the distinct impression that it rather abruptly controlled the diarrhea and decreased the evidences of toxemia.

Although not necessarily related to the type of infection just referred to, ulcerative colitis still represents, at least in certain phases, a serious

262. Marshall, E. K., Jr.; Bratton, A. C.; Edwards, L. B., and Walker, E.: Sulfanilylguanidine in Treatment of Acute Bacillary Dysentery in Children, *Bull. Johns Hopkins Hosp.* **68**:94, 1941.

263. Libby, R. L., and Joyner, A. L.: The Action of Sulfathiazole on the Colon-Typhoid-Dysenteriae Group of Organisms, *J. Infect. Dis.* **67**:67, 1940.

264. Villani, A. J.: Treatment of Infectious Diarrhea with Sulfapyridine, *West Virginia M. J.* **36**:414, 1940.

265. Welch, S. H.; Meyer, J., and Smith, J. S.: Acute Bacillary Dysentery Treated with Sulfapyridine, *J. M. A. Alabama* **10**:198, 1940.

and important form of intestinal infection. Inconstant results from the use of chemotherapeutic agents have been reported by various authors. Collins²⁶⁶ contributes his experience with sulfanilamide in 35 cases of ulcerative colitis and with azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3,' 6'-disulfonate) in 5 others. He attempts a careful analysis of the results obtained in cases of this serious condition and subdivides his cases in such a way that his conclusions seem reasonably well justified. He feels that a remission of the disease was probably attributable to the use of sulfanilamide in about one third of the 40 cases. He expresses a conservative opinion in stating that the drug has a place in the treatment of ulcerative colitis and should be used as an adjunct to the usual forms of treatment and not as a specific remedy. This would seem to be in entire agreement with the rather isolated and not too common experiences reported by various authors. Collins administered the drug by rectum, a form of administration which is probably limited to those cases in which the bowel is not too severely damaged or too irritable. It is certain that experiences with various forms of chemotherapy require further confirmation before any final decision is obtained as to the exact drug to be employed. Certainly in many instances of acute intestinal infection, and probably in many cases of chronic forms, particularly in those that are associated with the colon-typhoid-dysentery group of organisms, one or another of the derivatives of sulfanilamide may be used with real benefit to the patient. The exact route of administration also requires further study and observation. The vomiting so frequently associated with sulfapyridine is not necessarily related to direct irritation of the gastric mucosa, according to Sadusk, Hirshfeld, and Seymour.²⁶⁷ These authors state that animal experiments also show that the emesis associated with the use of this drug is not due to direct action on the vomiting center. That sulfapyridine does delay the emptying of the stomach is apparently proved by Northup and Van Liere.²⁶⁸ In the presence of serious vomiting due to the disease process, the intravenous or rectal administration of the drug is indicated and is feasible.

Therapeutic measures, other than chemotherapy, for infectious diarrheas have received less notice than in previous years. The results of bacteriophagic therapy of bacillary dysentery were studied by Viskovskiy.²⁶⁹ The author reports on over 3,500 patients with various forms

266. Collins, E. N.: Treatment of Chronic Ulcerative Colitis with Sulfanilamide, *Ann. Int. Med.* **14**:55, 1940.

267. Sadusk, J. F., Jr.; Hirshfeld, J. W., and Seymour, A.: Sulfapyridine and Vomiting, *Yale J. Biol. & Med.* **13**:351, 1941.

268. Northup, D. W., and Van Liere, E. J.: The Emptying Time of the Normal Human Stomach as Influenced by Sulfapyridine, *J. Pharmacol. & Exper. Therap.* **70**:297, 1940.

269. Viskovskiy, S. V.: Basic Principles in Bacteriophage Therapy in Bacillary Dysentery, *Sovet. vrach. zhur.* **44**:411, 1940.

of dysentery treated with bacteriophage during the last three years and contrasts the results obtained with those noted for a control group of 5,400 patients. Because bacteriophage has no antitoxic property, the author combined the use of this substance with specific serum therapy. He points out that bacteriophage is effective only in the early days of the disease and is probably of no value after the fifth day. Comparison of results in the two groups shows that in the one treated with bacteriophage the summer mortality did not increase, while in the control group it rose from 2.8 to 4.2 per cent. The mortality in the group whose infections were due to the Shiga bacillus was lowered three and a half times, as compared with the decrease in the control group; in the group whose infections were caused by the Flexner bacillus, the mortality was twice as high as in the control group, and in the group whose infections were caused by the Kruse-Sonne organism there was only 1 death. The author concludes that while the mode of action of the dysentery bacteriophage in a human organism has not been elucidated, its use as a therapeutic agent is superior to any one measure so far advanced. Such findings are of interest and will afford an important basis for comparison with the results that may subsequently be obtained by the use of chemotherapeutic agents.

Further observations on the beneficial effect of pectin on the milder forms of infectious diarrhea continue to appear. Kertesz and his associates²⁷⁰ consider that applesauce is extremely effective in curing an experimental form of infectious diarrhea produced in rats, provided the pectins are not digested by enzymes. The actual fate of ingested pectin was studied carefully by Werch and Ivy,²⁷¹ and if Kertesz and his associates are correct in concluding that the curative effect of applesauce depends on the pectin content, factors slowing the rate of its passage through the gastrointestinal tract should be avoided. Werch and Ivy show that the greatest content of pectin in the lower bowel is obtained when it is given alone, rather than with a meal. The greatest decomposition of pectin in man occurred when it was fed with a mixed diet, much larger amounts being recovered from the feces during fasting.

A most unusual form of intestinal infection is actinomycosis. The abdominal form of this disease is chiefly seen in connection with involvement of the cecum and the appendix or of the sigmoid. In the acute form it resembles appendicitis, whereas in chronic forms evidence of abscesses with perforation of the abdominal wall and fistulas finally develops, and these are usually the basis for identifying the condition.

270. Kertesz, Z. I.; Walker, M. S., and McCay, C. M.: The Effect of Feeding Applesauce on Induced Diarrhea in Rats, *Am. J. Digest. Dis.* 8:124, 1941.

271. Werch, S. C., and Ivy, A. C.: On the Fate of Ingested Pectin, *Am. J. Digest. Dis.* 8:101, 1941.

Six cases are reported by Dorling and Eckhoff²⁷² and Woodman.²⁷³ The use of sulfanilamide or sulfapyridine or both drugs apparently resulted in complete recovery in 4 cases.

Fungous infection of the gastrointestinal tract has been noted from time to time, and the report by Swartz and Jankelson²⁷⁴ on the incidence of fungi in the stools of patients with nonspecific ulcerative colitis is of moderate interest. These authors demonstrated comparatively pure cultures of *Geotrichum* in nearly 90 per cent of 24 patients with non-specific ulcerative colitis but in only one third of normal controls. They concluded that the finding of *Monilia albicans* in certain instances was of prognostic significance and denoted a malignant course. Inasmuch as fungi have been frequently obtained from patients suffering from sprue, pernicious anemia and other diarrheal conditions, it is doubtful that this observation is etiologically significant.

The wide prevalence of protozoal infections throughout the world is being more and more clearly recognized, and with the extension of hostilities to the Middle East and the tropics it has become important to facilitate studies on protozoal infection. Adler and Foner²⁷⁵ describe a simple medium suitable for the cultivation of *Entamoeba histolytica*, *Trichomonas intestinalis* and *Balantidium coli*. It can be tubed in 5 cc. amounts. The best results seem to be obtained if the medium, which is semisolid, is inoculated with a culture of *Bacillus prodigiosus* and used two days later. Snyder and Meleney²⁷⁶ describe a method of obtaining the cysts of *E. histolytica* free of living bacteria, which they employed in the cultivation and observation of parasites, with particular reference to the factors necessary for continued cultivation and normal multiplication.

Various surveys on the subject of parasitic infection may be mentioned briefly as indicating the incidence of these conditions and the interest in them in different parts of the world. An encouraging study is that by Keller and his associates,²⁷⁷ who report on comparative studies on hookworm in eight southern states. Surveys made during the years

272. Dorling, G. C., and Eckhoff, N. L.: Chemotherapy of Abdominal Actinomycosis, *Lancet* **2**:707, 1940.

273. Woodman, T. W.: Abdominal Actinomycosis, *Southwestern Med.* **25**:81, 1941.

274. Swartz, J. H., and Jankelson, I. R.: Incidence of Fungi in the Stools of Non-Specific Ulcerative Colitis (Preliminary Report), *Am. J. Digest. Dis.* **8**:211, 1941.

275. Adler, S., and Foner, A.: Culture of Intestinal Protozoa, *Lancet* **1**:243, 1941.

276. Snyder, T. L., and Meleney, H. E.: The Excystation of *Endamoeba Histolytica* in Bacteriologically Sterile Media, *Am. J. Trop. Med.* **21**:63, 1941.

277. Keller, A. E.; Leathers, W. S., and Densen, P. M.: Results of Recent Studies of Hookworm in Eight Southern States, *Am. J. Trop. Med.* **20**:493, 1940.

1930 to 1938 showed a striking reduction in infection of comparable groups in relation to that noted from 1910 to 1914. In the later period 11.2 per cent of all stools examined showed hookworm infection, a reduction of nearly 70 per cent over previous figures. Although the hookworm problem is still a major one, it is obvious that a great deal has been accomplished as a result of various public health measures in recent years. A survey of intestinal protozoa was made on 350 office patients by Beregoff-Gillow²⁷⁸ in Montreal. Protozoa in some form were found in over 10 per cent of all stools studied, and nine different varieties were encountered. *E. histolytica* was found in 2 per cent of the stools, *Dibothriocephalus latus* in 4 per cent, *Oxyuris* in 3 per cent and *Giardia* in 10 per cent. Obviously, such a report indicates the wisdom of careful stool examinations, even in northern climates; this point is further emphasized in a report from Toronto by Kuitunen-Ekbaum.²⁷⁹ Examinations of stools of 438 school children showed that 33 per cent harbored one or more species of intestinal protozoa or helminths. A still higher incidence was reported by Coutelen,²⁸⁰ for 649 healthy nursery school children in Lille and Douai, France. Seventy per cent of all the children studied showed parasites, and multiple infection was found in over half of them. As many as six varieties at times shared the human host. *Oxyuris* was the parasite most commonly found. Ro²⁸¹ examined the stools of 465 elementary school children in an agricultural district in Formosa and found the highest percentage of any one parasite to be that of *Ascaris lumbricoides*, 35 per cent in males and 10 per cent in females, although numerous other parasites were encountered. A single administration of santonin followed by senna and magnesium sulfate produced complete cure in children.

Amebiasis continues to be studied as a source of potential epidemics. Tsuchiya and Jean²⁸² examined 562 medical and dental students in St. Louis for intestinal protozoa over a six year period. Only 2 per cent of the students harbored *E. histolytica*, and none of them had symptoms. Such an incidence is slightly lower than that revealed by other surveys.

278. Beregoff-Gillow, P.: A Survey of Intestinal Protozoa in a Private Practice in Montreal, *Canad. M. A. J.* **43**:592, 1940.

279. Kuitunen-Ekbaum, E.: Intestinal Parasites in Children in Toronto, *Am. J. Dis. Child.* **60**:518 (Sept.) 1940.

280. Coutelen, F.: Incidence and Importance of Intestinal Parasitism in Early Infancy: Its Place in Preventive Medicine, *Presse méd.* **49**:29, 1941.

281. Ro, M.: Stool Examinations in Elementary School Children, with a Note on Santonin Treatment, *Taiwan Igakkai Zassi* **39**:1983, 1940.

282. Tsuchiya, H., and Jean, J. T.: The Incidence of Intestinal Protozoa Among Freshman Medical and Dental Students, with Especial Reference to Amebiasis, *Am. J. Trop. Med.* **20**:803, 1940.

In New Orleans, Faust²⁸³ investigated the incidence of amebiasis as revealed by autopsies on persons killed in accidents. *E. histolytica* was demonstrated in 6.4 per cent of 240 examinations made within four hours after death. In Chicago, Howell and Knoll²⁸⁴ established the diagnosis of amebiasis in 4 per cent of 408 children seen in hospital practice. The authors refer to somewhat similar figures, 4.8 per cent obtained from a survey in a Chicago orphanage. In the 18 children discussed by these authors various abdominal conditions obtained, and several of the children had symptoms so typical of acute appendicitis that only the early isolation of active amebas prevented operation.

The incidence of so-called nonpathogenic amebas on the production of clinical symptoms is still controversial. Rothman and Epstein²⁸⁵ consider this phase of parasitic infection and present their clinical observations on 406 patients harboring one or more of the five forms of human intestinal amebas. The most prevalent protozoan encountered was *Endolimax nana*, and *E. coli* was second in order of frequency. The authors consider that from a clinical point of view all forms of amebas appear to have a pathogenic role but properly conclude that the results of carbarsone therapy, which is effective against all forms, should be taken as an indication of the symptomatic importance of the findings in any given case. Certain figures are noted which indicate the magnitude of the problem. Surveys show that protozoa are the most prevalent of all human parasites, and reference is made to an estimation by Lynch that more than 30,000,000 people in the United States are infected with one or more of these organisms. According to Byrd (also cited by Rothman and Epstein), of this large number 2.5 to 10 per cent harbor *E. histolytica*, 15 to 31 per cent *E. coli*, 10 to 37 per cent *Endolimax nana*, 2 to 4 per cent *Iodamoeba bütschlii* and 2 to 4 per cent *Dientamoeba fragilis*. Too sweeping conclusions as to the pathogenicity of most of these protozoa are certainly not warranted, but such figures should properly give rise to serious speculation as to their importance and to indications for therapy.

The natural infections caused by *E. histolytica* in monkeys are of importance in relation to infection in human beings. Three separate species were found to be infected with *E. histolytica*, although there were no observable symptoms, and the situation seemed to be comparable in every respect to the carrier infections in man. The importance of the

283. Faust, E. C.: Amebiasis in the New Orleans Population as Revealed by Autopsy Examination of Accident Cases, *Am. J. Trop. Med.* **21**:35, 1941.

284. Howell, K. M., and Knoll, E. W.: Amebiasis in Infants and Children, *Am. J. Dis. Child.* **61**:54 (Jan.) 1941.

285. Rothman, M. M., and Epstein, H. J.: Clinical Symptoms Associated with the So-Called Non-Pathogenic Ameba, *J. A. M. A.* **116**:694 (Feb. 22) 1941.

report lies in pathologic studies which showed that even in the absence of symptoms and macroscopic lesions, microscopic examination of the infected intestine will often demonstrate invasion of the tissue on the part of the amebas. Johnson²⁸⁶ concludes that the information thus gained lends support to the belief that every carrier of *E. histolytica* should be treated, not only from the point of view of public health, but from the standpoint of his own good, since it is unlikely that any carrier escapes without some damage to the tissue.

A rather rare complication of amebiasis is mentioned by Wyatt and Buchholz.²⁸⁷ Two cases of gangrene and ulceration of the skin of the anterior abdominal wall due to infection with the parasite are presented, in both instances the lesions being due to drainage from an abscess of the liver. A résumé of the literature reveals 20 similar cases.

The importance in temperate zones of excluding amebic infection as a cause of ulcerative colitis is demonstrated by Beregoff-Gillow.²⁸⁸ Seven cases are recorded from Montreal, in none of which the stool was examined until two or three months after the initial complaint and in 5 of which colostomy was done.

The frequency of pinworm infection, or enterobiasis, is again attested by several studies. Weller and Sorenson²⁸⁹ found that one fifth of over 500 children examined in Boston were infected. They present a critical analysis of their figures, however, and feel strongly that the infection was relatively asymptomatic. They make it clear that symptoms may occur in this condition but point out that, as a rule, it exists as a sub-clinical entity. Similar swab studies were made by Cram²⁹⁰ in the District of Columbia, where, for the purpose of studying the incidence of familial pinworm infection, a total of 320 families (1,525 persons) were examined. In the white families multiple cases were the rule rather than the exception, and children were twice as frequently infected as adults. Single cases were found in slightly more than one half of the Negro families in which infection occurred, and it was generally noted that the incidence was much lower in Negro families than in white ones, especially among adults. Kuitunen-Ekbaum surveyed a group of 843 children in three institutions in Toronto. Nearly one half of all the

286. Johnson, C. M.: Observations on Natural Infections of *Endamoeba Histolytica* in Ateles and Rhesus Monkeys, *Am. J. Trop. Med.* **21**:49, 1941.

287. Wyatt, T. E., and Buchholz, R. R.: Amebiasis Cutis, *Ann. Surg.* **113**:140, 1941.

288. Beregoff-Gillow, P.: Amebic Dysentery and Ulcerative Colitis, *Canad. M. A. J.* **43**:588, 1940.

289. Weller, T. H., and Sorenson, C. W.: Enterobiasis: Its Incidence and Symptomatology in a Group of Five Hundred and Five Children, *New England J. Med.* **224**:143, 1941.

290. Cram, E. B.: Studies on Oxyuriasis: IX. Familial Nature of Pinworm Infestation, *M. Ann. District of Columbia* **10**:39, 1941.

children examined harbored *Oxyuris*, and in one institution the incidence was as high as 73 per cent. In Quebec Miller and Choquette²⁹¹ noted an incidence of pinworm infection of 33 per cent in children ranging from 6 to 16 years of age. In North Carolina, Brown, Sheldon and Thurston²⁹² examined by means of National Institute of Health swabs a total of 350 persons, chosen from three separate groups: 132 white boys ranging in age from 8 to 14 years from a fresh air camp; 100 white and Negro patients of all ages from the outpatient clinic at the Duke University School of Medicine, and 118 male students ranging in age from 17 to 31 years at the University of North Carolina. As in Cram's survey, the incidence of infection in white boys was much higher than in white adults. Seven per cent of all the white subjects were infected, although only 2.3 per cent of those over 20 years of age harbored the parasite. Not a single pinworm was found among the 33 Negroes examined or among the university students. Such comparative figures are of particular interest and raise the question whether the Negro may be partially immune to pinworm infection, as he is to hookworm infection. Similar findings were obtained by Sawitz²⁹³ and his associates in a study of nearly 500 children in New Orleans. In one institution the incidence was 97 per cent, although the total incidence in all institutions was much higher than the figures just quoted. The incidence among Negroes, only 16 per cent, conformed to that mentioned earlier in this paragraph. After the fourteenth year the percentage of pinworm infection definitely decreased.

Experiences with the treatment of oxyuriasis with gentian violet still seem to indicate that this drug is the most efficacious agent yet employed. Miller and his associates²⁹⁴ found it to be efficient in approximately 90 per cent of cases. Atabrine still seems to be the drug of choice in the treatment of *Giardia* infection, and confirmation of its usefulness is to be found in an article by Nutter and his associates.²⁹⁵ Manson-Bahr²⁹⁶ obtained excellent results in treating roundworm infec-

291. Miller, M. J., and Choquette, L.: Studies on Pinworm Infection in Canada: I. Incidence in French-Canadian School Children, *Canad. M. A. J.* **43**:453, 1940.

292. Brown, H. W.; Sheldon, A. J., and Thurston, T.: Incidence of Pinworm (*Enterobius Vermicularis*) Infection in North Carolina, *South. M. J.* **33**:922, 1940.

293. Sawitz, W.; D'Antoni, J. S.; Rhude, K., and Lob, S.: Studies on Epidemiology of Oxyuriasis, *South. M. J.* **33**:913, 1940.

294. Miller, M. J.; Choquette, L.; Audet, W.; Kelso, R. F., and Guenette, J. A.: Studies on Pinworm Infection: II. Tests with Gentian Violet in the Treatment of Pinworm Infection, *Canad. M. A. J.* **43**:455, 1940.

295. Nutter, P. B.; Rodaniche, E. C., and Palmer, W. L.: *Giardia Lamblia* Infection in Man, *J. A. M. A.* **116**:1631 (April 12) 1941.

296. Manson-Bahr, P.: Phenothiazene as Anthelmintic in Treadworm and Round Worm Infections, *Lancet* **2**:808, 1940.

tion with phenothiazine (a thiazine dye). The use of hexylresorcinol in the treatment of *Ascaris* and *Necator* infections is advocated by Ingling,²⁹⁷ who employed it in a group of Kentucky school children harboring these parasites.

Trichiniasis is a rare disease in Great Britain. For this reasons, a report by Garrod and Maclean²⁹⁸ and by Lee²⁹⁹ are of some interest, as they suggest that it may be more widespread than is generally recognized. Bercovitz³⁰⁰ discusses residual symptoms existing in patients after recovery from acute infection with trichinas. No residual symptoms were detectable after one month in three fourths of 70 patients examined; no symptoms persisted longer than a year, and in no case was there anything resembling permanent disability.

Deficiency Conditions.—The relation between vitamin deficiency and gastrointestinal disturbances is complicated, and at times avitaminosis may play a leading role in the production of organic changes and consequent symptoms. It is equally true, however, that frank avitaminoses occur because of existing disease and consequent modifications in diet.

Speculation has ranged between the two extremes of cause and effect in regard to the role of vitamin C deficiency in peptic ulcer. In most instances a moderate lack of ascorbic acid on the basis of blood determinations is evident in patients with chronic peptic ulcer. In all probability, this lack is due to a prolonged restriction of diet. That avitaminosis C plays any important role in the symptomatology of this condition is still far from proved, although the suggestion by Field and his associates³⁰¹ that it may contribute to serious gastric hemorrhage in patients with ulcer is a possibility that should not be overlooked. The levels of vitamin C in the blood reported by these investigators are no lower than those found in large groups of patients suffering from other diseases without associated hematemesis, but it certainly is conceivable that once an ulcer becomes active, healing is delayed or interfered with by subclinical scurvy, and this in turn may lead to frank hemorrhage. Their report on 2 frankly scorbutic patients without ulcer but with gross hematemesis enhances the value of such a suggestion, and one regrets that these patients were not examined gastroscopically to determine the exact appearance of the stomach. A few observations have already been

297. Ingling, H. H.: Clinical Study of Intestinal Parasites, Ohio State M. J. **36**:1083, 1940.

298. Garrod, L. P., and Maclean, D.: Trichiniasis in Hertfordshire, Brit. M. J. **1**:240, 1941.

299. Lee, J. E. S.: An Outbreak of Trichiniasis in Wolverhampton and District, Brit. M. J. **1**:237, 1941.

300. Bercovitz, Z.: Residual Symptoms in Patients Following Recovery from Acute Infestation with Trichinosis, Am. J. Trop. Med. **20**:849, 1940.

301. Field, H., Jr.; Robinson, W. D., and Melnick, D.: Vitamins in Peptic Ulcer, Ann. Int. Med. **14**:588, 1940.

made in which gross gastrointestinal bleeding has been thus visualized in scorbutic patients. In any event, the conclusion is sound that replacement therapy is indicated whenever there is any evidence of vitamin C lack in patients with ulcer, particularly because of its possible beneficial effect on healing. The authors indicate another difficulty that may contribute to the complexity of the ulcer problem, namely, the development of deficiency of vitamin B₁ in patients with ulcer receiving intensive alkali therapy. In vitro experiments indicate that a large proportion of thiamine hydrochloride incubated with bile and pancreatic juice at the natural p_H of these substances is destroyed. In patients, chemical evidence has been obtained of a deficiency of B₁ under prolonged alkali treatment. Inasmuch as vitamin B₁ deficiency may be initiated in a fairly short time, such a factor should not be overlooked.

A rather questionable set of deductions is to be found in a paper by Lucksch³⁰² on vitamin C and gastric function. He points out that vitamin C acts as a stimulus to the secretion of hydrochloric acid in the stomach and makes the rather broad suggestion that it may be of use in any instances of hyposecretory activity, including pernicious anemia. No control observations are given to corroborate such statements, but the suggestion may be of some value and should be checked by further studies.

One of the best and most balanced articles on the gastrointestinal symptoms incident to minor degrees of subclinical pellagra (nicotinic acid deficiency) is that by Field, Parnall and Robinson.³⁰³ They describe accurately the various symptoms that are frequently encountered in cases of mild pellagra. Lack of the antipellagra factor of the B complex may produce a whole range of gastrointestinal symptoms, from anorexia to all the disturbances associated with a so-called irritable colon. Special reference is made to one symptom, the importance of which is frequently overlooked, namely, epigastric and substernal burning during or shortly after the ingestion of food, particularly of acid food. Recognition of the possible existence of a vitamin B deficiency on the basis of such symptoms and a carefully taken dietary history cannot be too strongly emphasized, together with the fact that adequate doses of vitamin B complex administered under such circumstances will result in pronounced improvement in gastrointestinal symptoms in a few days. This article is of particular importance also because of its application to the average population of the northern states, where the recognition of pellagra is not so universal as it is in the South. The article is worthy of careful reading.

302. Lucksch, F.: Vitamin C and Gastric Function, *Wien. klin. Wchnschr.* **53**:457, 1940.

303. Field, H., Jr.; Parnall, C., Jr., and Robinson, W. D.: Pellagra in the Average Population of the Northern States, New England J. Med. **223**:307, 1940.

Mackie, Eddy and Mills³⁰⁴ have made a lengthy study on vitamin deficiencies in gastrointestinal disease. Because of advances in biochemical knowledge, particularly as regards enzyme activity and the breakdown of foodstuffs in intracellular metabolism, the problem of vitamin deficiency assumes a broad perspective. The function of the stomach and intestinal tract with the accessory organs of digestion and absorption places this system in a position of great importance with respect to vitamin deficiencies. Thus, any pathologic condition which interferes with normal food intake, normal digestion, normal absorption of the products of digestion or normal utilization of these products by the liver may produce secondary or conditioned avitaminosis. Primary deficiencies due to defective diet are not rare, and the authors comment on the fact that many dietary regimens in vogue are open to grave criticism. The authors' observations on the levels of vitamin A, carotene and ascorbic acid in the blood and on prothrombin time demonstrate that diets widely used in the treatment of peptic ulcer and ulcerative colitis are not adequate to maintain normal nutrition. Although the article is somewhat speculative, it presents an excellent review of the subject and a point of view that is well worth careful consideration by all who are interested in dietary or digestive disturbances.

The roentgenologic evidences of nutritional disturbances, with particular reference to the small intestine, are reviewed by Golden.³⁰⁵ He discusses not only primary changes, which are undoubtedly associated with damage to the intramural nervous system of the intestine, but changes secondary to preexisting disease of the digestive tract. With the present knowledge that lack of certain components of the vitamin B complex actually causes histologic changes in Auerbach's and in Meissner's plexus, these comments are of particular importance. Many of the changes to be noted by exact roentgenographic study are reversible and can be modified by careful attention to dietary needs. Valuable additional information regarding the nutritional state of a person may be obtained by special attention to the intestinal pattern as observed by the well trained roentgenologist. Golden also notes that protein lack and vitamin deficiency may produce similar abnormalities, a point already established by Ravdin, Rhoads and others.

Indirect evidence as to the importance of lack of vitamin B₁ in the regulation of the activity of the small bowel is to be found in the experiments of Dick and Hege,³⁰⁶ who poured solutions of thiamine hydro-

304. Mackie, T. T.; Eddy, W. H., and Mills, M. A.: Vitamin Deficiencies in Gastrointestinal Disease, *Ann. Int. Med.* **14**:28, 1940.

305. Golden, R.: Abnormalities of the Small Intestine in Nutritional Disturbances: Some Observations on Their Physiologic Basis, *Radiology* **36**:262, 1941.

306. Dick, M., and Hege, J. R., Jr.: The Effect of Thiamin on the Intestines of the B₁ Deficient Rat, *Am. J. Physiol.* **132**:636, 1941.

chloride through isolated strips of intestine of normal rats and of vitamin B₁-deficient rats. In the control group no alterations were noted, but in experiments on sections of ileum removed from vitamin B₁-deficient rats, peristalsis and tonus definitely increased within a short time after the addition of thiamine hydrochloride.

Albright and Stewart³⁰⁷ report an excellent detailed study of some of the changes that may occur during the course of uncontrolled diarrhea. The observations were made on a patient with chronic regional ileitis who had had a large proportion of the diseased ileum removed. Marked steatorrhea was present, which in turn prevented the absorption of all the fat-soluble vitamins. There resulted, therefore, hypovitaminosis D with hypocalcemia and tetany; hypovitaminosis K with severe bleeding diathesis and failure of the blood to clot; hypovitaminosis A with a low serum content of carotenoids, the precursor of vitamin A; xeroderma, and probably hypovitaminosis E, although there was no clinical or laboratory evidence of the last-named condition. The authors also point out that it is possible that the steatorrhea led to the disturbance in the steroid metabolism which resulted in an absence of 17-keto steroids from the urine. Furthermore, because of a deficiency in the protein metabolism, pituitary amenorrhea developed, with an absence of follicle-stimulating hormone in the urine. Finally, the intestinal anastomoses that were necessitated also led to a primary anemia similar to that in the cases reported by Barker and Hummel in 1939. It is emphasized that pan-fat-soluble vitamin deficiency should be looked for in all cases with chronic steatorrhea, regardless of the primary symptom. Patients with chronic steatorrhea should receive a low fat diet and when possible should obtain fat-soluble vitamins in fat-free vehicles. Although this paper represents a report of only 1 case, the studies were so well carried out and the conclusions so well considered that it is worth careful reading.

The clinical effects of prolonged steatorrhea are further emphasized in an article by Bennett and Hardwick³⁰⁸ on chronic jejunoileal insufficiency occurring in tropical sprue, celiac disease and similar conditions. The report represents the experience of the authors during the past twenty years and because they also studied the condition in children contains some additional manifestations not noted by Albright and Stewart. In their patients stunting of growth, with occasional infantilism and megacolon was accompanied by severe anemia and evidences

307. Albright, F., and Stewart, J. D.: Hypovitaminosis of All Fat-Soluble Vitamins Due to Steatorrhea: Report of Case, *New England J. Med.* **223**:239, 1940.

308. Bennett, T. I., and Hardwick, C.: Chronic Jejuno-Ileal Insufficiency: Pathogenesis of Celiac Disease, Tropical Sprue and Other Conditions, *Lancet* **2**:381, 1940.

of vitamin D deficiency. The latter manifested itself in the low figures for blood calcium and phosphorus and in the clinical signs of rickets. In the cases of tropical sprue, the well known blood change, macrocytic anemia, with stomatitis and glossitis, was commented on. In the cases of celiac disease, as a rule, the anemia was of the hypochromic variety, although changes in the buccal mucous membrane were common. The occurrence of a macrocytic type of anemia in regional ileitis is commented on by Plum and Warburg,³⁰⁹ who added further evidence to the frequently noted deficiency resulting from this condition.

An unusual cause of a deficiency state is that reported by Eisenstein³¹⁰ in a case of tetany secondary to the rather extreme use of cathartics. The patient, a woman aged 32, had been constipated since infancy, and a daily cathartic habit was well established by the age of 12. For two years before being seen the patient had gone from mild cathartics to the most drastic form of purgation and a daily dose of as many as 10 Hinkle pills (the equivalent of five to ten times the average U. S. P. dose of each ingredient [except cascara]: 0.15 Gm. aloin, 0.1 Gm. podophyllum, 0.15 Gm. extract of cascara sagrada, 0.08 Gm. extract of belladonna and 0.04 Gm. oleoresin of ginger). The resultant movements were violent and watery. Various nutritional disturbances had taken place in the nails, skin and teeth, and there was some numbness of the extremities. She also suffered from night blindness. The most striking symptoms, however, were full blown tetany of a year's duration, as evidenced by stiffness and muscle cramps, and difficulty in swallowing because of tetany in the facial and pharyngeal muscles. A low blood calcium level was associated with the clinical manifestations of tetany, which responded rapidly to the administration of dihydro-tachysterol. On the restoration of normal blood calcium levels, not only was the tetany controlled, but certain of its visceral manifestations disappeared, including the bowel cramps. Spontaneous bowel movements were restored with only minor measures, which previously had been ineffective. A further point of interest in relation to these extreme manifestations of vitamin A and calcium deficiencies was the history of definite nephrolithiasis. This condition is recognized as one of the possible complications of a deficiency in this particular fat-soluble vitamin.

Bean and Spies³¹¹ report on 100 persons in whom pellagra, beriberi and riboflavin deficiency developed as a complication of chronic diarrhea.

309. Plum, P., and Warburg, E.: Hematogenic Changes in Ileitis, Especially Megalocytic Forms of Anemia, *Ugesk. f. læger* **102**:467, 1940.

310. Eisenstein, V. W.: Chronic Adult Tetany of Gastro-Intestinal Origin, *Pennsylvania M. J.* **44**:33, 1940.

311. Bean, W. B., and Spies, T. D.: Vitamin Deficiencies in Diarrheal States, *J. A. M. A.* **115**:1078 (Sept. 28) 1940.

They point out the vicious circle involved in such diseases, stressing the fact that chronic diarrhea, in itself predisposes to the development of deficiency syndromes by causing increased loss and decreased absorption. Secondary deficiencies almost invariably improve once the diarrhea is relieved, even without vitamin therapy. The dosage of parenterally injected crystalline vitamins suggested by these authors is much higher than that ordinarily employed. They advocate the daily use of 500 to 1,000 mg. of nicotinic acid amide, 10 to 50 mg. of thiamine hydrochloride and 2 to 10 mg. of riboflavin. They also stress what is frequently forgotten, namely, that crystalline vitamin preparations are valuable but do not take the place of a high protein, high calory diet.

The conception that vitamin deficiency may lead to secondary complications of an infectious nature, as has been suggested in cases of ulcerative colitis, is borne out in part by the observations of Day and his co-workers.³¹² In animals placed on a vitamin M-deficient diet Day and his colleagues have confirmed results of previous experiments and have recovered *Shigella paradysenteriae* from the stools of monkeys under these conditions. They conclude from their results that vitamin M deficiency causes a lowered microbic resistance in the gastrointestinal mucosa and that gingivitis and ulcerative colitis result from the action of pathogenic saprophytes already present in these locations. Whether these results can be directly transferred to dysentery-like conditions in man is still a controversial matter, but such findings afford an excellent basis for speculation as to the mechanism of such diseases as ulcerative colitis. In this editorial comment several other articles are referred to which report similar studies and are of interest.

Lack of vitamin K in the presence of diarrhea has been recognized by various observers and has already been alluded to, but the report of Núñez and Sanguineti³¹³ is worthy of record in that in 35 cases of secondary intestinal tuberculosis, over one fourth of the patients showed marked reduction in plasma prothrombin. A still more striking reduction was present in 4 of the cases in which there was intestinal bleeding. A similar manifestation was also noted by Allen,³¹⁴ who confirmed the previous report of Butt and his collaborators of prothrombin deficiency in nontropical sprue.

Miscellaneous Considerations.—Among unusual causes of digestive symptoms is paralysis of the phrenic nerve, as described in a case report

312. Avitaminotic Dysentery, editorial, J. A. M. A. **116**:2169 (May 10) 1941.

313. Núñez, C. J., and Sanguineti, A. A.: Prothrombinemia in Secondary Intestinal Tuberculosis, *Prensa méd. argent.* **27**:2568, 1940.

314. Allen, J. G.: The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Non-Tropical Sprue, *New England J. Med.* **224**:195, 1941.

by Harper and Levin.³¹⁵ Distressing and persistent gastrointestinal symptoms developed after paralysis of the left side of the diaphragm, accentuated by left thoracoplasty. Roentgenograms of the stomach showed absence of any excursion of the left side of the diaphragm, elongation of the stomach in the perpendicular position and displacement of the pylorus and the first portion of the duodenum to the left. Fluoroscopy revealed that the stomach was fixed, while the movement of the pylorus with each respiration resulted in an acute angulation at the outlet of the stomach and partial and intermittent obstruction. The symptoms were successfully ameliorated by the introduction of pneumoperitoneum, since the introduction of air to the peritoneal cavity improved the anatomic relations of the stomach and duodenum.

A further example of the development of acute abdominal symptoms from pleuropulmonary disease is to be found in an article by Ruggieri.³¹⁶ This author reports 5 cases of acute abdominal symptoms simulating acute surgical conditions of the abdomen which resulted from acute purulent empyema in 3 cases, perforation of the collapsed lung in the course of artificial pneumothorax in the fourth case and perforation of the lung into the mediastinum in the fifth case. The underlying cause of the symptoms was verified by careful roentgenographic examination and by the observation that the symptoms were essentially associated with the process of respiration.

"Intra-abdominal apoplexy" is a rare condition due to massive spontaneous intraperitoneal hemorrhage resulting from the nontraumatic rupture of a small intra-abdominal blood vessel. One case is described by Berk and his colleagues,³¹⁷ and 19 similar cases reported in the literature are analyzed by them. The condition should be considered, according to these authors, in all cases in which there is a sudden, severe abdominal pain, with shock and signs of peritoneal irritation, especially in association with known hypertension and arteriosclerosis.

The protean manifestations of hypoglycemia are still imperfectly recognized and understood. Occasionally hypoglycemia results in abdominal pain or distress in the absence of other evidence of organic disease. The difficulty of establishing such a cause for recurrent attacks of abdominal pain is obvious, but the report of 5 cases by Sandler³¹⁸

315. Harper, F. R., and Levin, O. S.: Gastrointestinal Disturbances Following Phrenic Paralysis Relieved by Pneumoperitoneum, *Am. Rev. Tuberc.* **42**:130, 1940.

316. Ruggieri, E.: Acute Abdominal Syndrome from Empyema and Perforation of Lung, *Policlinico (sez. prat.)* **47**:1931, 1940.

317. Berk, J. E.; Rothschild, N. S., and Doane, J. C.: Intra-Abdominal Apoplexy, *Ann. Surg.* **113**:513, 1941.

318. Sandler, B. P.: Chronic Abdominal Pain Due to Hypoglycemia, *Surgery* **9**:331, 1941.

is of distinct interest. Surgical intervention, after a long period of recurrent attacks, failed to relieve symptoms. Appendectomy was performed in 3 cases, cholecystectomy in 1 case and herniorrhaphy in 1 case, but these procedures afforded no relief. Reexamination of the histories revealed that in all 5 cases nervous manifestations of hypoglycemia had not been accorded their proper significance and the results of dextrose tolerance tests were characteristic. Although such an explanation should not be accepted in any case until all other causes have been considered, there is little doubt that Sandler's observations are worthy of serious consideration.

Adhesions as a cause for abdominal pain have been too frequently accepted by physicians without hesitation or reluctance. In a large percentage of instances, such adhesions have proved a rather illusory foundation for observed symptoms and surgical procedures directed toward their removal have been extremely disappointing. The experience of McCann³¹⁹ in 23 cases of marked postoperative omental adhesions is, therefore, of interest. In this article a critical attitude is taken toward the relation between postoperative adhesions and abdominal symptoms, and the criteria which McCann lays down are so rigid as to leave little doubt that in these particular instances cause and effect were properly related. The author encountered three types of symptoms: 1. Reflex symptoms occurred while eating or within a half-hour after the intake of food and were associated with attacks of colic. These attacks were of short duration. 2. Symptoms referable to the colon consisted of colicky pain, intractable constipation and painful bowel movements with relief after defecation. These symptoms appeared to dominate the picture if the reflex disturbance was late in developing. 3. Symptoms referable to the peritoneum were due to constant tension and intermittent traction on the colon via the fixed omentum from the pull of physical effort. Roentgenologic evidence that adhesions might be the cause of symptoms was required by the author and involved the demonstration of dilatation, diminished haustration and elongation of the transverse colon, hyperperistalsis, segmental or focal spasm and delayed emptying. The article is well illustrated and seems to provide adequate basis for diagnosis and treatment.

The gastrointestinal symptoms attributed to allergic manifestations are frequently vague and difficult to define. Much of the literature is equally vague and inadequate. For this reason, any reports on carefully observed cases in which specific allergic reactions were the cause of serious gastrointestinal symptoms are of interest. Rubin³²⁰ stresses

319. McCann, J. C.: Omental Adhesions Syndrome: Postoperative Dysfunction of the Transverse Colon, *Surg., Gynec. & Obst.* **72**:707, 1941.

320. Rubin, M. I.: Allergic Intestinal Bleeding in the Newborn, *Am. J. M. Sc.* **200**:385, 1940.

intestinal hemorrhage in infants as a rather unusual and poorly described condition. He reports 6 cases that are practically identical, in which the infants had repeated attacks of abdominal colic and loose stools containing mucus and varying amounts of bright red blood. The onset of symptoms in each instance occurred within a few weeks of the commencement of feeding with cow's milk, or in 1 case with goat's milk. The symptoms were immediately relieved by the removal of milk from the diet. No bleeding was noted in any other part of the body. The severity of the reaction was indicated by colicky pains associated with large, easily visible peristaltic waves in the region of the stomach, suggestive of pylorospasm.

News and Comment

American Conference on Industrial Health.—The American Conference on Industrial Health, under the auspices of the American Association of Industrial Physicians and Surgeons, will hold its second annual meeting on November 5 and 6, at the Chicago Towers, Chicago.

The opening session will be a symposium on the technical problems of industrial health, based on the assumption that supervision of health in industry involves two great principles: (1) the adjustment of the working environment to the employee, and (2) the adjustment of the employee to the working environment, which includes the human environment.

In the afternoon a symposium on the economics of industrial health will include discussions of (1) the organization and the cost of a health service, and (2) the value of an industrial health service to the employer, to the employee and to the public.

On the morning of the second day a symposium on the social implications of industrial health will be followed by a discussion of how extensive an industrial health service should be; whether the hospital and medical care plans are related to industrial health service in any practical way; whether legislation plays a part in this problem; the evaluation of labor turnover, spoilage and lack of trained men, and the experiences of management and the interests of insurance carriers in the medical and social problems presented.

The conference will close with the inspection of a series of plant medical departments, made possible by special arrangement with local industries.

Book Reviews

Radiologic Physics. By Charles Weyl, S. Reid Warren Jr. and Dallett B. O'Neill. Price, \$5.50. Pp. 443, with charts and diagrams. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The authors of this book are all engaged in teaching the radiations courses in the curriculum of the Graduate School of Medicine of the University of Pennsylvania. Such courses are designed primarily for graduate students and fellows in radiology and dermatology. These men, therefore, should have firsthand information as to the needs, abilities and limitations of the physicians who would have occasion to use this book as a text or reference.

The authors state that the book is intended to serve as a thorough text on physics for radiologists. They also state that it has been their aim to develop a reasonably complete introductory text, with emphasis placed on simplicity and clarity, but no compromise has been made with the requirement of rigor. Within limitations and with certain exceptions their aim has been fulfilled. However, to attempt to bridge the gap between no knowledge and advanced specialization is a noble undertaking and is more than can reasonably be expected in a volume of this size. It would seem, therefore, that if this book is to serve the best purpose for which it is intended, i. e., a text on physics for the average radiologist, a compromise with the requirement of rigor might well have been made.

The book is divided into two parts: (1) the theory and practice of electrical engineering as applied to radiologic apparatus, and (2) the theory and application of radiation physics with reference to roentgen ray diagnosis and roentgen ray and gamma ray therapy. The first two chapters deal with theories and facts of physical phenomena, which can be found in any modern college physics textbook. They are well worth the space they occupy, however, and serve as a good review. The remainder of part 1, consisting of the next five chapters, deals with (1) electric circuits, (2) electrical measuring instruments, (3) transformers, generators and motors, (4) electronics and (5) electromedical apparatus. These chapters do contain all of the fundamental facts, but it would be difficult for the student of radiology, who usually is not entirely familiar with higher mathematics, to follow the trend of thought and to pick these facts out and digest them. It would seem that there is too much theory and not enough practical explanation.

The second part of the book is much better done and serves the purpose of the book to a much better advantage. It contains the facts that every practicing radiologist wants to and should know. Even here the reader may have such trouble following the trend of thought because of the theoretic derivations and long, redundant discussions leading up to a point that the point may be missed entirely. The subjects dealt with rather extensively are as follows: (1) theory of radiant energy, (2) interaction of roentgen rays and matter, (3) radioactivity and nuclear physics, (4) control of roentgen rays and gamma rays, (5) use of roentgen rays and gamma rays for therapy, (6) fluoroscopic and roentgenographic techniques and (7) variations of exposure factors. The last two chapters would be valuable to the technician or the practicing physician or surgeon who only occasionally uses roentgen rays for diagnostic purposes in his office.

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann, M.D., Ph.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Disease, United States Marine Hospital. Second edition. Price, \$5, cloth. Pp. 468, with 91 illustrations and 3 plates. St. Louis: C. V. Mosby Company, 1941.

This book is just what the author says it is in the preface to the first edition: a short cut to the solution of problems in cardiovascular disease. From this

standpoint it is an excellent little book. It is difficult to find anything of importance in the study of heart disease that has been omitted, although many things of importance are only mentioned and not discussed. This is sure to be true in a synopsis, and it is in the selection of material that the author of such a book meets his greatest test. Dr. Herrmann has done well, but it is likely that he will be criticized by those whose opinion in regard to the selection of material does not agree with his own.

His note on the implications and the significance of cardiovascular disease should be read by every medical student and young practitioner.

The book deals with the classification of heart disease, both anatomic and therapeutic. The criteria of the American Heart Association are discussed. The tools with which one must work, such as the stethoscope and the sphygmomanometer, are touched on. Electrocardiography is fairly considered.

The different forms of heart disease are dealt with briefly but adequately. A chapter on peripheral vascular disease has been added to the second edition, and the work is brought into harmony with the times by the addition of a chapter on *military cardiovascular examination and interpretation*. The illustrations are numerous and excellent. It is difficult to see why the author does not accord as much importance to hypertensive heart disease as he does to the rheumatic and syphilitic forms, but he discusses it fairly well. He is faced with the impossible task of getting too much into too small a space, but he comes as close as possible to success.

The advanced student of cardiovascular disease will not like this book because of its lack of bibliography and discussion, but the medical student and the general practitioner will find here answers to many of their questions.

Physical Medicine. By Frank H. Krusen, M.D., Associate Professor of Physical Medicine, the Mayo Foundation, University of Minnesota, and Head of the Section on Physical Therapy, the Mayo Clinic. Price, \$10. Pp. XVI + 846, with 351 illustrations. Philadelphia: W. B. Saunders Company, 1941.

This is a worth while undertaking: a textbook on physical medicine designed for students, practitioners and specialists. It is admirably planned, beginning with a fine historical account of how modern physical therapy came into being. There follow chapters devoted to various phases of physical therapy—heat, light, electricity, water, exercise, rest, massage, etc. Each chapter is delightfully written, telling the story so simply that the general reader finds it readily comprehensible, yet at the same time in such fashion that the expert can get helpful information. To combine what a highly trained specialist may wish to find in a new textbook on any phase of medicine with what the physician in general practice or the student ought to learn of an unfamiliar subject in so large a field requires great literary skill.

The author has been well trained in the art of medical writing and realizes the cardinal virtues of clarity, brevity and simplicity of style. At the same time he knows well the literature of his subject and has placed at the end of each chapter a carefully selected bibliography pertinent to the topic under discussion. Last, but not of least importance, are the illustrations. They help greatly to clarify the text by describing in pictorial form many of the methods currently used in various forms of physical therapy.

Physicians in general have been backward in realizing what an important adjunct to clinical work is well organized, skilfully performed physical therapy. The author points out that at present there are but sixteen approved schools for physical therapy technicians in the entire United States. Thus the two concluding chapters, which describe the proper teaching of physical medicine not only to technicians but to medical students and the organization of a department of physical therapy in a modern hospital, are especially significant to all teachers of medicine and to those who deal particularly with the perfecting of a smoothly running hospital machine.

On the whole, the book is a well balanced composition. It deserves a high degree of success.

Textbook of Pediatrics. By J. P. Crozer Griffith, M.D., Ph.D., and A. Graeme Mitchell, M.D. Third edition, revised and reset. Price, \$10. Pp. 991. Philadelphia: W. B. Saunders Company, 1941.

The present edition differs from the last one in several respects. First, it has a new title, being called "Textbook of Pediatrics" instead of "The Diseases of Infants and Children." Second, the authors have procured for the first time the assistance of numerous collaborators and authorities, both in and out of the field of pediatrics, who have contributed to, criticized or advised concerning the material used in this edition. Third, the bibliography, so prominent in the last edition, has been entirely eliminated from the present one. In this edition, much more than in the previous ones, the authors have emphasized the characteristics of good physical and mental health, prevention of disease and, especially, growth and development. Because much of the theoretic knowledge of disease has been omitted, and chiefly practical facts have been included, the book is easy to read and easy to understand. It is written concisely, in simple language, and many of the chapters have been rewritten to follow this style.

A good deal of new material has been added, including chapters on mental and emotional development, pediatric institutions and organizations and important symptoms of diseases of the respiratory tract. Additional information in the chapters on epidemic encephalitis, infectious diseases and poisoning is evident.

In general, all of the revisions, additions and changes in this new edition tend to make it a more practical and usable book. It may be recommended highly, not only as a textbook for students but as reference for general practitioners and pediatricians.

The March of Medicine. Price, \$2. Pp. XII + 154. New York: Columbia University Press, 1941.

Medical knowledge has considerable appeal to many persons other than physicians and nurses. Well edited publications like *Hygeia* are one means of satisfying such popular curiosity. Medical lectures by doctors to college students or other lay audiences afford another appropriate vehicle for bringing before the public medical items of general interest.

Annually for five years the New York Academy of Medicine has offered a course of medical lectures to the laity. These lectures have been deservedly successful for they have been given by men who are capable in the subjects selected for discussion, who possess the knack of picturesque expression and who are able to speak concisely and clearly. This booklet reprints six of the lectures which were offered by the Academy during 1940.

The topics chosen cover a wide field: mental disease, chemotherapy, hematology, virus disease and bronchoscopy. Each of these subjects in itself is of general interest. To a doctor or teacher, however, the stimulating part of the book does not lie in the choice of subject but rather in the manner in which it has been presented. It is fascinating to observe how an authority like Perrin Long, for instance, can talk to a nonmedical audience about chemotherapy or to read the romantic story of bronchoscopy as told by Chevalier Jackson to an audience outside the medical profession.

Physicians in various communities who are concerned with the public lecture plan can learn many tricks of the trade from a careful study of this unassuming little volume. For a doctor to give to a layman any medical lecture that is interesting, truthful and worth listening to is something of a feat. This book shows how it should be done.

Ueber die Häufigkeit von Krankheiten: Tuberkulose, Ulkuskrankheit und Krebs. By Dr. F. Reichert. Price, 1.35 marks. Pp. 48, with 7 illustrations. Leipzig: Georg Thieme, 1941.

This small volume of 48 pages is a statistical analysis of the morbidity and mortality of tuberculosis, gastric and duodenal ulcer and cancer in Berlin and other parts of Germany. The statistics are chiefly those of 1937 and 1938. No total or

comparative death rates from tuberculosis and cancer over a period of years are given. Death from ulcer of the stomach and duodenum throughout the Reich increased in the proportion of 100 in 1932 to 120 in 1936. Comparative statistics indicate that the death rate from tuberculosis was considerably higher and that from ulcer much lower among printers than among the general population. The relative incidence of pulmonary tuberculosis and of gastric and duodenal ulcer throughout the Reich was 28 to 83 among males and 24 to 23 among females. Comparative statistics pertaining to these three diseases in 21 cities of Germany show that in 1937 and 1938 Dresden had the highest incidence of tuberculosis, up to 7.6 per thousand of the population in the age group from 40 to 49; that in Cologne the incidence of gastric and duodenal ulcer reached the surprising number of 23.4 per thousand in the age group from 30 to 39, and that Nuremberg led all these cities, with an incidence of cancer of 5.12 per thousand men over 40 years of age, while in Solingen there was an incidence of 9.5 per thousand men over 60. This book may interest those concerned with vital statistics. The value would have been increased if more actual statistical data had been included.

Dietetics for the Clinician. By Milton A. Bridges. Fourth edition. Price, \$10. Pp. 960, with 83 tables. Philadelphia: Lea and Febiger, 1941.

This elaborate and comprehensive book on dietetics was reviewed in the *ARCHIVES* several years ago (40:177 [July] 1937). The criticisms then expressed still hold to some extent, although the work contains a vast amount of useful information. Since Dr. Bridges' death, a group of collaborators have prepared this fourth edition and have done their work extremely well. They have vastly improved the book, especially the discussions of diet with reference to special diseases. The immense amount of tabular data on foods remains invaluable for reference.

A Textbook of Ophthalmology. By Sanford R. Gifford. Second edition. Price, \$4. Pp. 470, with 215 illustrations. Philadelphia: W. B. Saunders Company, 1941.

The reviewer, not being a professional ophthalmologist, is unable adequately to criticize certain parts of this book. He is impressed, however, with the fact that here in small space are given the essentials of ophthalmology in concise and readable form. The illustrations are well executed and abundant, and there are useful diagrams concerning both optical and other matters. The writer has dealt well not only with topics pertaining locally to the eye but with the relation of ophthalmology to internal medicine.

The Avitaminoses. By Walter H. Eddy and Gilbert Dolldorf. Second edition. Price, \$4.50. Pp. 519. Baltimore: The Williams & Wilkins Company, 1941.

The speed of new developments in this field is well brought out by the changes in this book since the first edition, only four years ago. Entirely new vitamins have been discovered; chemical formulas then unknown are now definitively described, and symptoms and signs of deficiencies previously vague are now clearly presented. The writers have obtained a happy combination of clinical and laboratory material, with excellent bibliographies. As matters stand at present the book seems a thorough and up-to-date summary.

SIGNIFICANCE OF BACTEREMIA CAUSED BY STAPHYLOCOCCUS AUREUS

A STUDY OF ONE HUNDRED AND TWENTY-TWO CASES AND A REVIEW
OF THE LITERATURE CONCERNED WITH EXPERIMENTAL
INFECTION IN ANIMALS

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AND

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Within recent years there has been an increasing interest in the various aspects of infections caused in both man and animals by *Staphylococcus aureus*. In order to gather more information concerning the factors that influence the course of these infections in man, we have studied a group of 122 cases of bacteremia in which the causative agent was *Staph. aureus*. We were especially interested in analyzing these cases in the light of experimental infections as they have been produced in animals by numerous investigators.

ANALYSIS OF CASES

The 122 cases were observed at the Boston City Hospital over a seven year period. In all cases, the patients had demonstrable bacteremia on one or more occasions and the clinical course was entirely consistent with a severe infection. In only 22 cases did the patients recover, a fatality rate of 81.97 per cent.

Seasonal and Sex Incidence.—There was no peak of incidence at any season of the year, although there were a few more cases in the winter and in the summer than at other seasons. In 66 per cent of cases the patients were males and in 34 per cent females, with the same relative number of deaths in each sex group, 63 and 37 per cent, respectively.

Age Incidence.—Most of the patients (67.2 per cent) were under 40 years of age, with the extremes at 10 weeks and 72 years. In 57

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per cent of the cases bacteremia occurred during the second, third or fourth decade, the greatest number being in the second (27, 16 and 13 per cent, respectively). Of the 40 patients over 40 years old, only 1 recovered, whereas 77 per cent of the recoveries occurred in patients younger than 30 years (fig. 1). The influence of the age of the patient on other factors concerned with the bacteremia will be discussed presently.

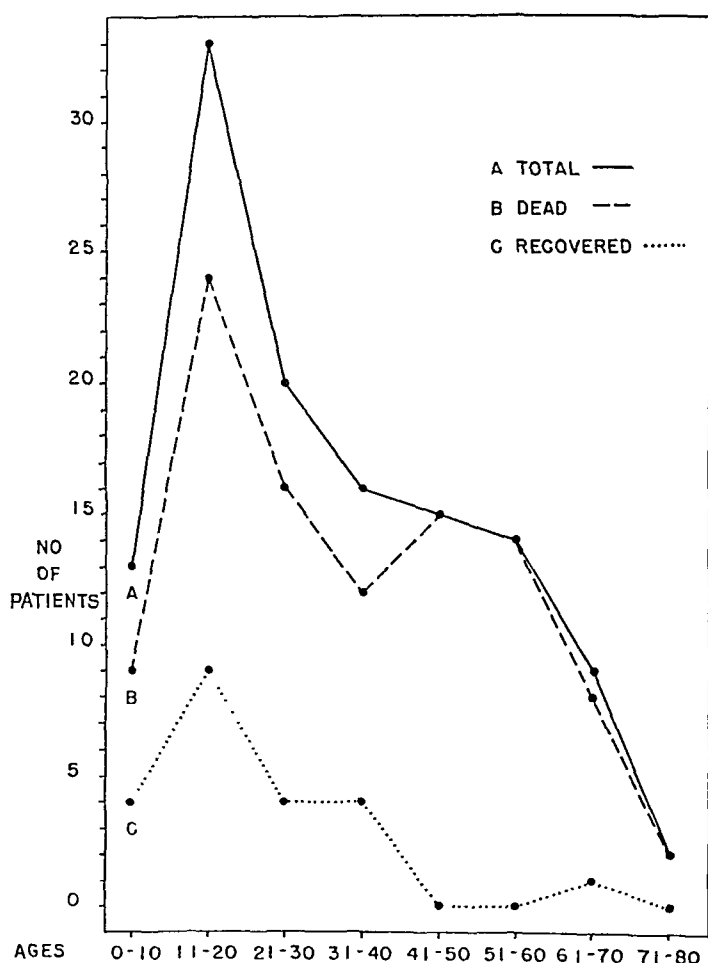


Fig. 1.—Age incidence of patients surviving and recovering in 122 cases of bacteremia caused by *Staph. aureus*.

Portal of Entry.—There were four common portals of entry for the agent causing bacteremia: the skin, the respiratory passages, the bones and the genitourinary tract. In 12 cases the portal of entry was undetermined (table 1).

Of the 57 cases in which the portal of entry was the skin, in 24 the infected area was located on the face, head or neck. In only 1 case of the 24 did the patient, who had a carbuncle on the neck, recover. The

location of the infection in 17 cases was the lower extremity, and in 4 the patient recovered. The types of lesions may be listed as follows:

	No. of Cases
Boils and carbuncles.....	30
Infected wounds	14
Infected vesicles	9
Areas of cellulitis.....	2
Infected areas of arteriosclerotic gangrene.....	2

In 17 cases it seemed clear that bacteremia followed a rupture of the local defense mechanism. In 10 of them the primary abscess was

TABLE 1.—*Portal of Entry of Organism in One Hundred and Twenty-Two Cases of Bacteremia Caused by Staphylococcus Aureus*

Portal of Entry	Number of Cases			Mortality Rate, Per Cent
	Total	Recovery	Death	
A. Skin.....	57	8	49	86.0
Face.....	12	0	12	
Head.....	4	0	4	
Neck.....	8	1	7	
Hand.....	3	0	3	
Arm.....	5	1	4	
Foot.....	2	0	2	
Leg.....	6	0	6	
Hip.....	2	1	1	
Thoracic wall.....	1	0	1	
Abdominal wall.....	1	1	0	
Vesicle.....	7	3	4	
Multiple.....	6	1	5	
B. Respiratory tract.....	30	4	26	86.7
Infections of the upper respiratory tract.....	20	3	17	
Pneumonia.....	5	0	5	
Sinusitis.....	2	1	1	
Peritonsillar abscess.....	1	0	1	
Otitis media.....	1	0	1	
Empyema.....	1	0	1	
C. Bone.....	11	5	6	54.5
Primary osteomyelitis.....	11	5	6	
D. Genitourinary tract.....	11	3	8	72.7
Puerperal sepsis.....	3	0	3	
Pyelonephritis.....	4	2	2	
Infection of the prostate gland.....	3	1	2	
Cystitis.....	1	0	1	
E. Circulatory system				
Phlebitis.....	1	1	0	00.0
F. Unknown.....	12	1	11	91.7

surgically incised, and in 7 the infected area was rubbed, squeezed or picked.

In 30 cases the respiratory passages were the portal of entry. Of 20 patients who had infections of the upper respiratory passages, only 3 recovered. Five patients had primary pneumonia, and they all died. None gave a history of a preceding infection of the upper respiratory tract. A peritonsillar abscess, otitis media and empyema were the source of infection in 1 case each; in all 3 cases the patient died. Of the 2 patients with sinusitis 1 recovered and 1 died.

In the 11 cases of "primary" osteomyelitis no history of a preceding staphylococcal infection was obtained, although in 5 of them there was a history of mild trauma, e. g. striking the knee a few days before the onset of the signs of infection.

Of the 11 cases in which the portal of entry was the genitourinary tract, there were 3 of puerperal sepsis. In 2 of them infection followed an abortion. In the other 8 cases the condition occurred in males. Three patients had an abscess of the prostate gland, and 1, cystitis. Three patients had acute pyelonephritis, and 1 recovered; bacteremia developed in another during the course of chronic pyelonephritis, but the patient recovered. In 2 of these patients bacteremia appeared after urethral instrumentation.

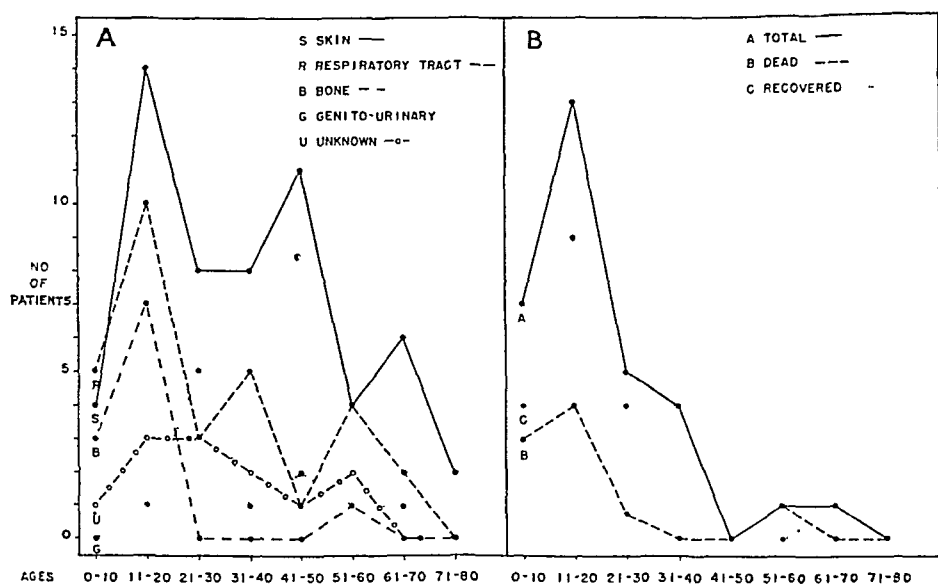


Fig. 2.—Relation of age incidence of patients to (A) portal of entry and (B) occurrence of focalized infections in 122 cases of bacteremia caused by *Staph. aureus*.

There was no relation between the season and the portal of entry, except in the case of the respiratory tract. Of 30 cases in which the infected area was in the respiratory tract, the infection in 10 began in the winter and in 10 it began in the spring.

However, there was some relation between the portal of entry and the age of the patient. In general, the age incidence with reference to each portal of entry parallels that of the entire series (fig. 2 A). The most striking correlation between the portal of entry and the age of the patient occurred among those for whom the portal was the skin, the respiratory tract or bone; the greatest incidence was in the second decade. In the group of patients with infections of skin there was a secondary peak of incidence in the fifth decade and in the group with

osteomyelitis, in the sixth, whereas in the group with infections of the respiratory tract the incidence declined with increasing age, except for a slight rise in the sixth decade. The 3 patients with puerperal sepsis were in the third decade of life. The other patients in whom the portal of entry was the genitourinary tract were all in the decades from the second to the seventh, inclusive; there was no peak of incidence in any one decade. The 1 patient with phlebitis was in the seventh decade, and the patients for whom a portal of entry could not be determined were evenly distributed throughout the first six decades.

Course and Clinical Features.—The average duration of the infection was thirty-three days, the shortest being two days and the longest three hundred and twenty-eight days. Of 47 patients whose illness lasted ten days or less, all died. Of the 29 patients surviving longer than thirty-three days, 18 recovered. The illness of most of the patients who recovered took a prolonged course after the infection was focalized in areas amenable to surgical drainage. There was no direct relation between age and the duration of the disease, although the course was more protracted in the younger patients who recovered.

Thirty patients had chills, and the majority (82 per cent) of patients had remittent fever (with temperatures constantly higher than 101.1 F.); some (14 per cent) had intermittent fever (with temperatures which were normal or subnormal to higher than 101.1 F. daily), and a few (4 per cent) had continuous low grade fever (with temperatures always less than 101.1 F.). A larger number of patients with high remittent fever died than did those with other types of fever.

Metastatic Infections.—Secondary infection occurred in 100 cases (82 per cent), while in 22 (18-per cent) there was none. In 12 cases (9.8 per cent) there was a direct extension of the primary focus, the most common being thrombosis of the sinuses of the intracranial vault.

Of the metastatic infections, pneumonia and superficial abscess were the most common. Less common were internal abscess, which could be diagnosed clinically, and osteomyelitis. In 36 patients multiple metastatic infections appeared. These various types of secondary infection are summarized in table 3.

There was no correlation between the portal of entry and the appearance of secondary infection. It was noted, however, that a metastatic abscess developed more commonly in patients with superficial abscess of the skin than in those with "primary" osteomyelitis. It was also found that a superficial abscess followed an infection of the respiratory tract as frequently as did pneumonia (table 2). The relation of age to the occurrence of metastatic infection is recorded in figure 2 B.

Local Abscesses Treated Surgically.—In 31 patients the infection was focalized after the onset of bacteremia, so that an abscess developed

TABLE 2.—*Relation of Secondary Infection to Portal of Entry*

Secondary Infection	Portal of Entry				Number of Cases and Outcome				
	Skin	Respiratory Tract	Bone	Genitourinary Tract		Total	Recovery	Death	Mortality Rate, Per Cent
				Puerperal Sepsis	Other Types of Infection				
None.....	8	5	4	1	2	22	2	20	90.9
Direct extension.....	8	2	0	1	1	12	0	12	100.0
Sinus thrombosis.....	6	1	0	0	0	7	0	7	
Meningitis.....	2	1	0	0	0	3	0	3	
Peritonitis.....	0	0	0	1	1	2	0	2	
Metastatic infection									
Pneumonia.....	20	10	2	1	1	37	0	37	100.0
Meningitis.....	2	1	0	0	0	7	0	7	100.0
Erysipelas.....	2	4	0	0	0	6	1	5	83.3
Acute endocarditis.....	1	0	0	1	0	7	0	7	100.0
Acute pericarditis.....	1	2	1	0	0	4	1	3	75.0
Empyema.....	1	2	0	0	0	3	0	3	100.0
Superficial abscess *.....	14	10	3	0	4	33	10	23	69.7
Skin.....	12	5	2	0	1	22	8	14	
Joints.....	2	4	0	0	2	8	1	7	
Muscles.....	0	1	1	0	1	3	1	2	
Internal abscess.....	12	5	0	0	2	21	5	16	76.2
Cerebral.....	3	1	0	0	0	5	0	5	
Pulmonary.....	3	2	0	0	0	5	0	5	
Epidural.....	2	0	0	0	1	3	1	2	
Pelvic.....	1	1	0	0	0	2	1	1	
Perinephritic.....	2	0	0	0	0	2	2	0	
Pyonephrotic.....	1	0	0	0	1	2	0	2	
Pretracheal.....	0	1	0	0	0	1	0	1	
Thyroiditis.....	0	0	0	0	0	1	1	0	
Osteomyelitis.....	9	5	0	0	0	14	8	6	42.9
Multiple metastases.....	17	11	2	1	1	36	5	31	86.1

* With associated phlebitis, 1 case.

which was amenable to surgical treatment (table 3). These patients had localized collections of pus in the skin, the subcutaneous tissue, the muscles, the bones or the pleural cavity. In all 22 patients who recovered the infection was focalized into superficial abscesses, with no demonstrable deep infections. All of these patients who recovered received surgical treatment, except 1. In this patient thyroiditis developed but subsided without surgical intervention. The fatality rate for these 31 patients was lower (29 per cent) than that for the entire series (81.97 per cent).

The majority (93.5 per cent) of the patients in whom foci of infection developed were under 40 years of age; only 2 were over 40, and 1 of them recovered. The age incidence of these patients parallels that of the entire series.

TABLE 3.—*Incidence of Localized Infection Following Bacteremia Originating at Various Portals of Entry*

Portal of Entry	Incidence			
	Complete Series		Localized Infection	
	Number of Cases	Percentage of Cases	Number of Cases	Percentage of Cases
Skin.....	57	46.7	12	38.7
Respiratory tract.....	30	24.6	7	22.6
Bone.....	11	9.0	7	22.6
Genitourinary tract				
Puerperal sepsis.....	3	2.5	0	00.0
Other types of infection.....	8	6.6	3	9.7
Circulatory system (phlebitis).....	1	0.8	1	3.2
Unknown.....	12	9.8	1	3.2
Total.....	122		31	

The portals of entry for these 31 patients were also of the same relative frequency as were those for the entire series, except that here there was a slightly smaller number of persons with infected areas of skin as the portal and a moderately greater number with osteomyelitis as the source of bacteremia.

The course of the disease among these patients was similar to that of the series as a whole, except that the duration was longer. With 1 exception all those patients whose infection could be focalized and who survived for thirty days recovered, although many had a protracted illness. This 1 patient died in a secondary wave of bacteremia, which apparently arose from the chronic osteomyelitis resulting from the primary wave.

Factors Influencing Bacteremia.—Several factors influenced the occurrence and the course of the bacteremia. For purposes of discussion they can be divided into two groups, dealing with (1) the nature

and management of the primary focus, and (2) the presence of debilitating diseases, such as diabetes, arteriosclerosis, heart disease and cancer (table 4).

One of the factors concerned with the pathogenesis of bacteremia was the rupture of the local defense mechanism by the incision of an abscess. There were 21 cases of such a rupture, and in only 2 did the patient recover. In most cases the infection was localized in the skin in the form of a furuncle or a carbuncle, which usually had been incised shortly before the development of bacteremia. In 1 case a peritonsillar abscess had been opened; in 1 empyema had been drained; in 1 a toe nail had been removed from a gangrenous toe, and in 7 a small furuncle had

TABLE 4.—*Factors Influencing Portal of Entry and the Outcome of Bacteremia*

Factors	Portal of Entry						Number of Cases and Outcome		
	Skin	Respira- tory Tract	Bone	Genitourinary Tract		Un- known			
				Puer- peral Sepsis	Other Types of Infection				
							Total	Recovery	Death
Rupture of local defense mechanism.....	19	2	0	0	0	0	21	2	19
Wound.....	13	0	0	0	2	0	15	0	15
Trauma.....	11	0	5	2	0	1	19	8	11
Diabetes mellitus.....	6	1	0	1	0	1	9	0	9
Arteriosclerosis.....	6	3	0	0	0	0	9	0	9
Heart disease.....	7	8	0	1	0	2	18	1	17
Arteriosclerotic.....	4	3	0	0	0	0	7	0	7
Rheumatic.....	1	4	0	0	0	2	7	0	7
Hypertensive.....	2	1	0	1	0	0	4	1	3
Cancer.....	0	1	0	0	0	0	1	0	1

been squeezed. Two of these patients had diabetes, and 1 had arteriosclerosis. Bacteremia following the rupture of the local defense mechanism occurred at all ages, an age incidence paralleling that of the entire series. In 7 of the patients pneumonia developed, and in 6 the infection spread by direct extension from the primary focus to the surrounding tissues (table 5.). The experience with these patients would serve to emphasize the dangers of rupturing the local defense mechanism of the body once an abscess has formed and the necessity of great care in draining such an abscess without injury to the surrounding tissues.

There were 15 cases of infection of a wound, with associated bacteremia, and in all cases the patient died. In 7 cases the wound was traumatic in origin; in 2 it was a trophic ulcer, in 2 the result of an abortion and in 1 the result of another type of operation. Of the other 8 cases, the infection in 1 followed a bite by a mouse, in 1 an insect bite and in 1 a liberal covering of a herpes simplex with lipstick. In 2

of these cases there were no metastases; in 2 there was a direct extension of the primary infection, and in 5 pneumonia and metastatic abscesses developed.

The development of bacteremia following traumatic injury without interruption of the continuity of the skin was observed in 19 cases, with 11 deaths. The injury was often mild, and the precise relation of trauma to infection was difficult to ascertain. In 7 cases vesicles of the skin became infected, and in 2 of them the blebs were incised before the appearance of the bacteremia. Cellulitis appeared in 1 case after an application of liniment to the thoracic wall, in another after an application of petrolatum to a bruised nose and in a third case after

TABLE 5.—*Conditions Preceding and Metastatic Infections Following Bacteremia*

Preceding Conditions	Metastases							
	None	Direct Extension	Pneumonia	Pneumonia with Associated Conditions *	Superficial Abscess	Internal Abscess	Osteomyelitis	Multiple Abscesses
Rupture of local defense mechanism.....	3	6	7	a	4	1	3	6
Wound.....	2	2	5	0	3	2	1	2
Trauma.....	6	0	3	b	6	1	5	4
Diabetes mellitus.....	4	0	1	a	4	1	0	2
Arteriosclerosis.....	3	0	4	a	2	1	0	2
Heart disease								
Arteriosclerotic.....	2	0	4	a	1	0	0	1
Rheumatic.....	1	0	2	c, d, e	0	1	1	2
Hypertensive.....	1	0	1	a	1	0	0	1
Cancer.....	1	0	0	0	0	0	0	0

* The following symbols have been used: a, erysipelas, 1 case; b, empyema, 1 case; c, meningitis, 1 case; d, acute pericarditis, 1 case, and e, acute endocarditis, 3 cases.

an accident which injured the leg. Of the cases of infections of the genitourinary tract bacteremia appeared in 2 after repeated passage of sounds or catheters; in another case cystitis, and later bacteremia, appeared after a fall which caused multiple fractures of one leg. Five patients had "primary" osteomyelitis and gave a history of mild trauma to the involved bone a few days before the onset of bacteremia but denied having a preceding infection. A mild blow to an old focus of infection in the thumb appeared to have reactivated the infection and given rise to bacteremia in 1 case. In 6 of these cases there were no metastases; in 6 there were metastatic superficial abscesses, and in 5 secondary osteomyelitis developed.

The presence of debilitating diseases was of significance in both the development and the outcome of the bacteremia. There were 9 patients with diabetes mellitus and bacteremia, and all of them died. The portal of entry was an area of infection of the face or neck in 4 cases,

an infected foot in 1 case, an infected prostate gland in 1, the skin (multiple boils) in 1 and an undetermined source in 1. Two of the patients who had an abscess of the face had the abscess opened before the onset of the bacteremia. In 1 the infected area was surgically incised, and in the other it was traumatized by squeezing. Four patients had arteriosclerosis, and 2 of them also had heart disease. Six of the diabetic patients were women and 3 were men; all were over 30 years of age, 56 per cent being over 50.

High grade arteriosclerosis was a predisposing factor in 9 cases. In 6 the portal of entry was an area of superficial infection of the skin; in the other 3, the respiratory tract. One patient had the nail removed from a gangrenous toe before the onset of bacteremia, and in another bacteremia followed a hatchet wound. Four patients also had diabetes, and 7 had arteriosclerotic heart disease as well. All the patients were in the seventh or the eighth decade of life, except 1 aged 49, who had a coronary occlusion during the course of bacteremia.

Heart disease was present in 16 patients, who could be divided into three groups: those with rheumatic, those with arteriosclerotic and those with hypertensive heart disease. The second group, in which there were 7 patients, includes some of those discussed in the preceding paragraph. There were 7 patients with rheumatic heart disease. By age they were evenly distributed throughout the second, third and fourth decades of life. The portal of entry was an area of superficial infection of the skin in 1, an unknown portal in 2, and an area of infection in the upper respiratory tract in the other 4. In the first patient acute bacterial endocarditis developed, with meningitis and osteomyelitis. Of the next 2 patients, acute bacterial endocarditis developed in 1 and subacute bacterial endocarditis in the other. Two of the others died of acute bronchopneumonia, and 2 had fulminating septicemia, with questionable acute pericarditis in 1 instance. There were 4 patients with hypertensive heart disease, 2 of whom also had arteriosclerotic heart disease. One of the other 2 died of sepsis and shock after a traumatic amputation of a leg. The fourth patient, aged 49, had hypertensive heart disease secondary to pyelonephritis and renal insufficiency. A large abscess formed; a culture of the blood was found to be positive for *Staph. aureus*, and the abscess healed.

One patient had a bronchiogenic carcinoma with (secondary) chronic empyema. Suddenly bacteremia developed, and he died.

TREATMENT

The treatment in these 122 cases varied from year to year. General supportive measures, blood transfusions, surgical drainage of foci of infection, administration of antitoxin and chemotherapy were used in different cases (table 6). Of the 75 patients receiving only general

treatment, 63 died, a fatality rate of 84 per cent. Thirty-two had supportive treatment alone, and 9 also received blood transfusions; all 41 died. Two of the 16 patients having supportive and surgical treatment alone recovered, while 8 of 15 patients receiving supportive treatment, surgical treatment and blood transfusions recovered. The fatality rates in these two groups were 87.5 and 46.7 per cent, respectively. Four patients received antitoxin, but they all died. Of the 34 patients receiving sulfanilamide and the 8 receiving sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) 9 recovered, a fatality rate of 78.6 per cent.

Every one is in agreement that the fatality rate in patients with staphylococcic bacteremia is high, and, regardless of the treatment which has been recommended, the fatality rate has been recorded as between 53 and 91 per cent by several groups of physicians.

TABLE 6.—*Treatment in One Hundred and Twenty-Two Cases of Bacteremia Caused by Staphylococcus Aureus*

Treatment	Number of Cases and Outcome			Mortality Rate, Percentage
	Total	Recovery	Death	
General.....	75	12	63	84.0
Supportive.....	32	0	32	
Supportive and transfusion.....	9	0	9	
Supportive and surgical.....	16	2	14	
Supportive, transfusion and surgical	15	8	7	
General and nonspecific agents.....	3	2	1	
General and antitoxin.....	4	0	4	100.0
General and sulfanilamide.....	34	9	25	73.5
General and sulfapyridine.....	8	0	8	100.0

From the experiences that have been reported with reference to infection in animals and from the recorded experience with reference to infection in man, it would appear that the following methods of treatment should be recommended: (1) administration of antitoxin for the neutralization of circulating toxin; (2) blood transfusions to supply red cells and leukocytes; (3) surgical drainage of all foci of infection, and (4) the use of large amounts of sulfapyridine or sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole).

COMMENT ON CLINICAL CASES

In summing up, then, one is justified in saying that bacteremia caused by *Staph. aureus* is of grave significance since it is followed by a high fatality rate. The common sources for invasion of the blood are the skin, the respiratory tract, the bones and the genitourinary tract. In a few cases it is not possible to determine the portal of entry. Bacteremia is frequently preceded by a rupture of the local defense mechanism by such measures as traumatizing a focus of infection, and

it is more frequent and serious in elderly patients with arteriosclerosis, diabetes or heart disease.

On the basis of the clinical course of illness the cases could be divided into four groups: those showing (1) bacteremia with no metastatic infection and rapid death, 20; (2) bacteremia with metastatic abscess and death, 70; (3) clearance of bacteremia with metastatic abscess and death, 10, and (4) clearance of bacteremia with drainage of metastatic abscess and recovery, 22.

Metastatic lesions were common and occurred in 82 per cent of the cases. When metastatic lesions failed to appear, the course of the disease was usually rapid and death occurred within two to ten days after the appearance of the first symptoms. In 2 cases of "primary" osteomyelitis no metastases were discernible, the infection being localized to the primary site and the patient recovering. Undoubtedly in such cases the "primary" osteomyelitis is an infection which is secondary to that at some undetected portal of entry. The commonest metastatic lesions were found in the skin, in the subcutaneous tissues and in the lungs. Although abscesses in other tissues were not infrequent, inasmuch as we selected for study a group of patients who had demonstrable bacteremia, the numerous cases of staphylococcic abscess in such organs as the kidney and the perirenal tissues and in other organs in which bacteremia was not demonstrable were not included. If one had an opportunity of following all cases of such abscess from the beginning of the infection, it might be possible, in many at least, to detect bacteremia early in the course of the disease and before the development of an abscess. Those cases would then fall into groups 3 and 4 as just described.

When recovery takes place, the blood stream is cleared of organisms and either the focus of infection which is responsible for the bacteremia is drained or a metastatic abscess is focalized and drained. This is observed more often in patients under 40 years of age than it is in older ones.

In the group of patients who recovered, the illness ran a protracted course on account of metastatic infection. In the group of patients who died the duration of illness was usually less than thirty days, and the largest number died in the first ten days.

Up to the present time, the treatment of staphylococcic bacteremia is unsatisfactory. The use of blood transfusions, with surgical drainage of purulent foci of infection, was the only form of therapy that seemed to be at all helpful, but even with this treatment the fatality rate remained over 50 per cent (53.3 per cent). It is interesting that there are no significant differences between the fatality rate for the whole series (81.97 per cent), that for the portion in which sulfanilamide or sulfapyridine (78.6 per cent) was given and that for the remainder (83.8 per cent).

REVIEW OF THE LITERATURE CONCERNING ANTIGENIC STRUCTURE
AND ANIMAL EXPERIMENTATION

In view of the foregoing observations, it was of interest to review the important experimental work dealing with infections caused by *Staph. aureus*. The antigenic structure of the staphylococcus, so far as it is known, is summarized in table 7.

The cultural characteristics of the staphylococcus were studied forty to fifty years ago and are too well known to need further description. More recently an attempt has been made to correlate the biologic characteristics of the organism with its virulence. It has been found that its pathogenicity is more accurately determined by its antigenic power than by its cultural characteristics.¹ One of the best single cultural tests of virulence is that of mannitol fermentation, which Julianelle² claimed is accurate for at least 95 per cent of all strains. Chapman and his co-workers³ stated that the pathogenicity of a given organism can be determined with a high degree of accuracy by correlation of three of its properties, color, coagulase production and hemolytic activity, and that the best of these for a single test is coagulase production.

The problem of staphylococcic dissociation and the relation of this phenomenon to virulence has just been attacked, and as yet the conclusions are not clearly defined. By means of type-specific precipitins Julianelle and associates separated staphylococci into two types, A and B, of which type A is pathogenic.⁴ Thompson and Khorazo⁵ divided the nonpathogens into at least two groups. Hoffstadt and

1. (a) Julianelle, L. A.: Studies of Hemolytic Staphylococci: Hemolytic Activity, Biochemical Reaction, and Serologic Reactions, *J. Infect. Dis.* **31**:256-284, 1922. (b) Panton, P. N.; Valentine, F. C. O., and Dix, V. W.: Staphylococcal Infection and Antitoxin Treatment, *Lancet* **2**:1180-1183, 1931.

2. Julianelle, L. A.: Determination of Types of Staphylococcus by Fermentation of Mannite, *Proc. Soc. Exper. Biol. & Med.* **36**:117-119, 1937.

3. (a) Chapman, G. H.; Berens, C.; Peters, A., and Curcio, L.: Coagulase and Hemolysin Tests as Measures of Pathogenicity of Staphylococci, *J. Bact.* **28**:343-363, 1934. (b) Chapman, G. H.; Berens, C.; Nilson, E. L., and Curcio, L. G.: The Differentiation of Pathogenic Staphylococci from Non-Pathogenic Types, *ibid.* **35**:311-334, 1938.

4. (a) Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci: I. Occurrence of Serologic Types, *J. Exper. Med.* **62**:11-22, 1935. (b) Wieghard, C. W., and Julianelle, L. A.: The Immunological Specificity of Staphylococci: II. The Chemical Nature of the Soluble Specific Substances, *ibid.* **62**:23-30, 1935. (c) Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci: III. Interrelationships of Cell Constituents, *ibid.* **62**:31-37, 1935. (d) Julianelle, L. A., and Hartmann, A. F.: The Immunological Specificity of Staphylococci: IV. The Cutaneous Reactions to the Type-Specific Carbohydrate, *ibid.* **64**:149-159, 1936.

5. (a) Thompson, R., and Khorazo, D.: Antigenic and Biochemical Properties of Staphylococci, *J. Bact.* **33**:51-52, 1937; (b) Correlated Antigenic and Biochemical Properties of Staphylococci, *ibid.* **34**:69-79, 1937.

TABLE 7.—Summary of Data Concerning the Antigenic Structure of the *Staphylococcus*

Organism	Constituents	Structure	Antigenicity	Thermal Resistance	Biologic Properties	Author
Whole.....					Pathogenicity; pigment production; agglutinability	Kolle and Otto (Ztschr. f. Hyg. u. Infektionskr. 41: 369-379, 1902)
P.....		Protein	+		Common to gram-positive cocci	Lancefield (J. Exper. Med. 42: 397-412, 1925). Julianelle and Wieghard. ^{4a} Wieghard and Julianelle. ^{4b} Julianelle and Wieghard. ^{4c}
C.....		Carbo- hydrate	0	Stable	Type-specific; haptene; types A, B and C	Julianelle and Wieghard. ^{4a} Wieghard and Julianelle. ^{4b} Julianelle and Wieghard. ^{4c} Thompson and Khorazo. ⁵
Capsule.....			+	Stable	Found in 3 hr. broth cultures of toxigenic strains; not formed during growth in serum; grows within leukocytes; destroyed by shaking; resists phagocytosis	Lyons. ²⁶
Toxin					Existence questioned	Spink. ²⁷
α hemolysin.....			+	Labile	Hemolyzes human, sheep and rabbit red cells; dermonecrotic and intravenous lethal properties (possibly identical)	Kraus and Clairmont (Wien. klin. Wchnschr. 13: 49-56, 1900). Julianelle and Wieghard. ^{1a}
α hemolysin.....			+	? Stable	Hemolyzes rabbit red cells; dermonecrotic for guinea pigs	Dolman and Kitching (J. Path. & Bact. 41: 137-162, 1935)
α ₂ hemolysin.....			+	? Stable	Hemolyzes rabbit red cells; end point of titration displaced	Morgan and Graydon. ⁸
β hemolysin.....			+	Labile	Found especially in bovine strains; hot-cold lysin for sheep red cells; nonlethal; causes flush on intradermal injection	Bigger, Boland and O'Meara (J. Path. & Bact. 30: 271-277, 1937). Glenn and Stevens (ibid. 40: 201-210, 1935)
α β hemolysin.....			?	?	Found in human and bovine strains; causes α hemolysis of rabbit red cells, β hemolysis of sheep red cells	Bryce and Rountree. ¹⁶
γ hemolysin.....			+	Labile	Hemolyzes sheep and rabbit red cells; differs from α and β hemolysins; may be identical with α ₂ hemolysin	Flaum and Forssman. ⁹ Smith. ¹⁰ Smith and Price. ¹¹
Dermatonecrotic.....			+	Labile	Intradermal injection causes necrosis (rabbit and guinea pig)	Parker (J. Exper. Med. 40: 761-772, 1924), Burnet. ¹³
Intravenous lethal.....			+	Labile	Intravenous injection causes sudden death (mouse, guinea pig, rabbit)	Burnet. ¹³ Kraus and Pribram (Wein. klin. Wchnschr. 19: 493-494, 1906)
Leukocidin.....			+	Labile	Destroys rabbit leukocytes; probably identical with hemolysin ¹²	Van de Velde (Cellule 10: 401-460, 1891). Neisser and Wechsberg (Ztschr. f. Hyg. u. Infektionskr. 36: 299-319, 1901)
Leukocidin.....			+	?	Destroys human leukocytes.....	Panton and Valentine. ¹³
Gastrointestinal.....			+	Labile	Oral ingestion produces symptoms of acute food poisoning	Dack, Carey, Woolpert and Wiggers (J. Prev. Med. 4: 167-176, 1930). Jordan, Dack and Woolpert (ibid. 5: 383-386, 1931). Jordan. ²⁴
Coagulase.....		? Enzyme	0	Stable	Coagulates plasma (human, horse, ox, sheep, guinea pig, etc.)	Loeb (J. M. Research 10: 407-419, 1903). Much (Biochem. Ztschr. 41: 143-155, 1908). Cruckshank. ^{25b}
Fibrinolysin.....		? Enzyme	0	Stable	Destroys fibrinogen and fibrin in hours or days (slowly destroys clot)	Much, Fisher (Bull. Johns Hopkins Hosp. 59: 415-426, 1936)

Youmans⁶ and Chapman and associates,^{3b} among others, have shown that dissociants of decreasing virulence can be produced from a virulent strain of staphylococcus. Hoffstadt and Youmans stated that, as shown in their earlier work, these dissociants have a lighter color and less hemolytic and coagulating power. Attempts by Hoffstadt and Clark⁷ to analyze chemically the structure of virulent and of avirulent staphylococci are as yet inconclusive.

The staphylococcic toxin which has received the most attention and against which antisera are tested is the hemolysin. This toxin hemolyzes rabbit, sheep and human red cells, the rabbit cells being the most sensitive and the human the least sensitive. The experimental results are confused by the use of different strains of organisms and different species of cells. For instance, the bovine strains of staphylococci produce the most β hemolysin, while human strains produce the most α hemolysin. The entire action of Morgan and Graydon's α_1 and α_2 hemolysins⁸ has not yet been determined. Flaum and Forssman⁹ have described another hemolysin which differs from both α and β lysin.¹⁰ Smith and Price¹¹ termed this the γ hemolysin and stated that it may be identical with the α_2 hemolysin. Panton and Valentine¹² claimed that hemolysin for human red cells probably differs from that which is active against rabbit cells. It would appear, then, that one of the toxic substances elaborated by the staphylococcus hemolyzes erythrocytes and is antigenic and that its action varies with the strain employed and the species of red cells that are used in the test.

The dermatonecrotic and intravenous lethal toxins require no special comment, except that the precise mechanism for the action of the lethal toxin is not known.¹³ Kellaway and associates,¹⁴ studying the

6. Hoffstadt, R. E., and Youmans, G. P.: *Staphylococcus Aureus*, Dissociation and Its Relation to Infection and Immunity, *J. Infect. Dis.* **51**:216-242, 1932.

7. Hoffstadt, R. E., and Clark, W. M.: The Chemical Composition and Antigenic Properties of Fractions of the Smooth and Rough Strains of *Staphylococcus Aureus*, *J. Infect. Dis.* **62**:70-82, 1938.

8. Morgan, F. G., and Graydon, J. J.: Toxins of the *Staphylococcus*, with Special Reference to Estimation of Potency, *J. Path. & Bact.* **43**:385-401, 1936.

9. Flaum, A., and Forssman, J.: Studies on *Staphylococci*: V. Experimental Investigations of Staphylolysin, *Acta path. et microbiol. Scandinav.* **13**:263-272, 1936.

10. Smith, M. L.: Circulating Antitoxin and Resistance to Experimental Infection with *Staphylococci*, *J. Path. & Bact.* **45**:305-310, 1937.

11. Smith, M. L., and Price, S. A.: *Staphylococcus* γ Hemolysin, *J. Path. & Bact.* **47**:379-393, 1938.

12. Panton, P. N., and Valentine, F. C. O.: Staphylococcal Toxin, *Lancet* **1**:506-508, 1932.

13. Burnet, F. M.: The Exotoxins of *Staphylococcus Pyogenes Aureus*, *J. Path. & Bact.* **32**:717-734, 1929.

14. Kellaway, C. H.; MacCallum, P., and Tebbutt, A. H.: The Fatalities at Bundaberg, Report of the Royal Commission, *M. J. Australia* **2**:2-30 and 38-64, 1928.

Bundaberg disaster, noted that the toxin was noxious to heart muscle and caused circulatory collapse. From later pharmacologic studies Kellaway and other co-workers¹⁵ concluded that the lethal toxin causes circulatory obstruction in the lungs and acts directly on the heart by constricting the coronary vessels, with resultant diminution of the coronary flow. However, he stressed the artificial conditions established by the necessary laboratory procedures.

The possibility that there is a single toxin with hemolytic, dermatonecrotic and lethal manifestations rather than three separate and distinct toxins is still being debated. Considerable suggestive, but no conclusive, experimental evidence has been presented to prove or disprove the unitarian viewpoint. Burnet,¹³ Bryce and Rountree¹⁶ and Levine,¹⁷ among others, found that results of quantitative studies of the different toxins were strictly parallel for each strain studied, while still others for example, Burky¹⁸ and Forssman,¹⁹ noted quantitative and qualitative differences among the toxins.

The results of the experimental studies of staphylococcic leukocidin have been confusing and inconsistent. This is due, in large part, to the use of leukocytes from different animals.¹² Valentine²⁰ expressed the belief that the leukocidal action against rabbit leukocytes is probably due to the hemolysin. This view was shared by Wright.²¹ On the other hand, both Valentine and Wright expressed the opinion that the leukocidin against human cells is distinct from hemolysin. They based their conclusions on the difference in the mode of destruction of the leukocytes as observed under the microscope. Proom²² has also noted

15. Kellaway, C. H.; Burnet, F. M., and Williams, F. E.: The Pharmacological Action of the Exotoxin of *Staphylococcus Aureus*, *J. Path. & Bact.* **33**: 889-912, 1930.

16. Bryce, L. M., and Rountree, P. M.: Production of β -Toxin of *Staphylococci*, *J. Path. & Bact.* **43**:173-189, 1936.

17. Levine, B. S.: The Unity of the Hemolytic, Dermonecrotic, and Lethal Properties of *Staphylococcal* Exotoxin and of Their Corresponding Counterparts in *Staphylococcal* Antitoxin, *J. Path. & Bact.* **48**:291-298, 1939.

18. Burky, E. L.: Studies on Cultures and Broth Filtrates of *Staphylococci*, *J. Immunol.* **24**:93-114, 1933.

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20. Valentine, F. C. O.: Further Observations of the Role of the Toxin in *Staphylococcal* Infection, *Lancet* **1**:526-531, 1936.

21. Wright, J.: *Staphylococcal* Leucocidin (Neisser-Wechsberg Type) and Antileucocidin, *Lancet* **1**:1002-1004, 1936.

22. Proom, H.: The Interrelationships of *Staphylococcal* Leucocidins, *J. Path. & Bact.* **44**:425-429, 1937.

this difference in the action of leukocidin on human and on rabbit cells. There is evidence that leukocidin is antigenic, and it is not difficult to believe that antileukocidal substances play a great part in the control of staphylococcic infections.

The gastrointestinal toxin is the toxin concerned in outbreaks of staphylococcic food poisoning. It is produced only by certain strains, which, however, cannot be differentiated by cultural or by biochemical tests from those strains which do not produce enterotoxin.²³ The earlier investigations, based on experiments with human volunteers, rabbits and *Macaca rhesus* monkeys, have been expanded recently by means of Dolman's method of intra-abdominal injection of the toxin into kittens, and results show that this toxin has definite and specific antigenic properties and differs from α and β toxins.²⁴

Coagulase and fibrinolysin are not true exotoxins and probably are enzymic; probably coagulase acts like thrombin and fibrinolysin destroys fibrin and fibrinogen.²⁵

Of the aforementioned bacterial constituents and toxins, probably all except the β hemolysin²⁰ are concerned in human infections, the α_1 and α_2 hemolysins being considered as α hemolysin. The enterotoxin probably is involved only in infections with certain strains, as is the fibrinolysin which also acts so slowly as to be of questionable effect.^{25b} The analogy has often been drawn between the dermonecrotic effect in experimental infections and the progress of events in surface infections in human beings. As yet the role of the lethal toxin in infections in man has not been worked out.

The role of hemolysin in infections in human beings is not fully understood. In certain cases of severe infection marked anemia and jaundice develop, a fact which could be explained on the basis of the action of hemolysin. Panton and Valentine¹² studied a group of strains from different sources and titrated the production of hemolysin and of

23. Kupchik, G. J.: Some Cultural and Biochemical Characteristics of Enterotoxic *Staphylococci*, *J. Infect. Dis.* **61**:320-324, 1937.

24. (a) Dack, G. M.; Jordan, E. O., and Woolpert, O.: Attempts to Immunize Human Volunteers with *Staphylococcus* Filtrates That Are Toxic to Man When Swallowed, *J. Prev. Med.* **5**:151-159, 1931. (b) Woolpert, O. C., and Dack, G. M.: The Relation of the Gastro-Intestinal Poison to Other Toxic Substances Produced by *Staphylococci*, *J. Infect. Dis.* **52**:6-19, 1933. (c) Dolman, C. E., and Wilson, R. J.: Experiments with *Staphylococcal* Enterotoxin, *J. Immunol.* **35**:13-30, 1938. (d) Jordan, E. O.: The Production by *Staphylococci* of a Substance Causing Food Poisoning, *J. A. M. A.* **94**:1648-1650 (May 24) 1930.

25. (a) Fisher, A. M.: The Plasma Coagulating Properties of *Staphylococci*, *Bull. Johns Hopkins Hosp.* **59**:393-414, 1936. (b) Cruickshank, R.: *Staphylocoagulase*, *J. Path. & Bact.* **45**:295-303, 1937.

leukocidin. The results fell into four groups, the four possible combinations being:

1. Leukocidin high, hemolysin low
2. Leukocidin high, hemolysin high
3. Leukocidin low, hemolysin high
4. Leukocidin low, hemolysin low

Strains falling in group 1 were found to be commonly associated with severe (pyemic) infections, whereas those in group 3 were associated with the superficial, sycotic type of infection of the skin. Later Valentine²⁶ showed that patients with corresponding infections had antiserum titers in the proportions which would be expected from a study of the different strains. These observations are of interest in the light of the recent studies of Lyons.²⁶ He expressed the belief that the capsules of young organisms are not formed during growth in serum and that the organisms are phagocytosed by a nonspecific opsonin. Within the leukocyte they produce a capsule and secrete their toxins; by destroying the cell they are again liberated into the blood stream.²⁷

Forssman,²⁸ on the basis of clearance experiments, stated that when suspensions of staphylococci are injected intravenously into normal rabbits the organisms are rapidly phagocytosed by the reticuloendothelial cells. This was most noticeable in the liver, spleen and bone marrow, which contain the greatest number of such cells. Colony counts of such organs are high immediately after injection and drop rapidly. Contrasted with this are the colony counts from heart and muscle, which are low at first and increase with elapsed time, despite the appearance of leukocytes in such areas. In normal animals the colony counts of blood show a steady increase after a slight initial drop.

26. Lyons, C.: Antibacterial Immunity to *Staphylococcus Pyogenes*, Brit. J. Exper. Path. **18**:411-422, 1937.

27. In recent studies Spink (Attempts to Demonstrate a Surface Antigen of *Staphylococci* and Specific Phagocytosis, Proc. Soc. Exper. Biol. & Med. **40**:549-552, 1939) has failed to demonstrate capsules in the staphylococcus and has found the bactericidal power of the blood of patients with chronic staphylococcic infection to be of low titer or to be entirely absent. That is to say, a patient may have an active localized infection without any bactericidal antibodies demonstrable in the circulating blood by the whole blood technic. The interpretation of these observations will require further studies, since it is not unlikely that the leukocytes are destroyed and hence the presence of antibodies may not be demonstrable by this method.

28. Forssman, J.: (a) Studies on *Staphylococci*: IX: On the Mechanism in Staphylococcal Infection and Immunity, Acta path. et microbiol. Scandinav. **14**: 468-477, 1937; (b) Staphylokokkenstudien: X. Verbreitung der Staphylokokken in Kaninchen nach intravenösen Injektionen von Staphylokokken, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**:165-175, 1937.

In animals immunized with toxoid—principally α hemolysin—the blood is not cleared, but there is no secondary increase in the bacteremia and the survival time is prolonged.²⁹ Lyons²⁶ presents experimental evidence showing that in animals the serums from which contain specific agglutinins for encapsulated organisms the bacterial counts can be reduced further than the initial clearance. Immunization with vaccine also prolongs the survival time,³⁰ but vaccine, probably because of its indeterminate toxin content, is not so effective an agent as toxoid.¹² In treatment of the more superficial types of staphylococcic infections in rabbits³¹ and in human beings,¹² vaccine therapy has little effect, whereas toxoid therapy has been more successful in treatment of such infections in man³² if the toxin content of the toxoid used is that which corresponds to the type of infection under treatment.¹² Valentine and associates³³ have reported encouraging results in a small series of cases of staphylococcic septicemia in which treatment was with a toxoid or an antitoxin of high antileukocidal and moderate antihemolytic titers. More recently Julianelle,³⁴ using type A staphylococcic antiserum, has succeeded in sterilizing the blood stream of 11 of 13 patients with septicemia caused by *Staph. aureus*.

In short, experimental septicemia in animals may take one of four courses:

1. Normal animal: bacteria partially cleared by reticuloendothelial system; secondary wave of bacteremia; no localization; death.
2. Animal immunized with toxoid: bacteria partially cleared; no secondary wave; abscesses; death.
3. Animal immunized against capsular antigen: bacteria largely cleared; no secondary wave; abscesses; death or survival.
4. Animals the serums of which contain capsular agglutinins, antitoxin and antileukocidin: bacteria cleared; abscesses; survival.

GENERAL COMMENT

The clinical course of staphylococcic infections in human beings and that of the experimental infections in animals are similar in many respects.

29. Burnet.¹³ Smith.¹⁰

30. Cowan, S. T.: Staphylococcal Infection in Rabbits: Antibacterial and Non-Specific Immunity, *J. Path. & Bact.* **48**:545-555, 1939.

31. Downie, A. W.: A Comparison of the Value of Heat Killed Vaccine and Toxoid as Immunizing Agents Against Experimental Staphylococcal Infection in the Rabbit, *J. Path. & Bact.* **44**:573-587, 1937.

32. Whitby, L. E. H.: The Treatment of Staphylococcal Skin Lesions with Toxoid, *Lancet* **1**:1454-1456, 1936.

33. Pantou, Valentine and Dix.^{1b} Valentine.²⁰

34. Julianelle, L. A.: Observations of the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia, *Ann. Int. Med.* **13**:308-316, 1939.

A survey both of the clinical cases of staphylococcic bacteremia reported herein and of records of experimental infections shows that several conditions are necessary for recovery. The blood stream must be cleared of bacteria and the infection focalized so that the infection can be treated by surgical drainage or be allowed to resolve spontaneously. This happens more often in a young person under 30 years of age. It must be emphasized that a certain number of patients die from the effects of infection even though their blood streams are cleared of organisms. In these patients the soluble products ("toxins") of the staphylococci are probably important. Presumably, in the patients who recover the "toxins" are neutralized, as well as the organisms destroyed. After the Bundaberg disaster Burnet¹³ reemphasized the importance of the toxins produced by the staphylococci and showed experimentally that hemolytic, dermatonecrotic and lethal toxins were formed *in vivo*. However, immunization against these toxins does not protect animals against experimental infection. Panton, Valentine and Dix³⁵ demonstrated the role of leukocidin and the importance of antileukocidin in experimental infections and in infections in human beings, but even this antibody did not overcome the bacteremia in the cases which they reported. Forssman²⁸ has stressed the importance of the reticuloendothelial cells in the clearing of the blood. Finally, Lyons²⁶ has demonstrated capsules on young staphylococci and the fact that the blood stream is cleared in animals the serums of which agglutinate such capsulated organisms.

The evidence, then, while incomplete, indicates that recovery occurs in man only if the blood is cleared of organisms, the infection localized into abscesses and the "toxic" effects of the infection neutralized. The animals with experimental bacteremia recover only if the reticuloendothelial system is active and the serum is able to protect the leukocytes from leukocidin by means of antileukocidin and to aid phagocytosis and the clearing of the blood stream. In addition, the hemolytic, dermatonecrotic and lethal toxins must be neutralized by their respective antiserums.

SUMMARY AND CONCLUSIONS

The cases of 122 patients with bacteremia caused by *Staph. aureus* were studied, and the literature concerning the antigenic structure of the organism and experimental infections with the staphylococcus was reviewed.

Of the 122 patients, only 22 recovered, a mortality of 81.97 per cent.

35. Panton and Valentine.¹² Panton, Valentine and Dix.^{1b} Valentine.²⁰

There was no correlation between the season of the year or the sex of the patient and the occurrence of bacteremia.

The majority of the patients recovering were under 30 years of age.

There was no definite correlation between the portal of entry and the outcome. The most frequent portals of entry were the skin, the respiratory tract, the bones and the genitourinary tract, cases of puerperal infection included.

There was some correlation between the age of the patient and the portal of entry. When the portal was the skin, the respiratory tract or the bone the greatest incidence was in the second decade. In the cases of two portals, the skin and the bone, there were secondary peaks of incidence in the fifth and the sixth decade, respectively.

Of the patients who died, more did so in the first ten days of illness than in any other ten day period. Conversely, the illness of those recovering ran a protracted course.

The most constant clinical feature was the presence of high, remittent fever, which decreased after surgical treatment of an abscess.

Treatment was unsatisfactory. The best results were obtained by the drainage of an abscess, when possible, and by blood transfusions.

Secondary infection appeared in 82 per cent of the cases. In 9.8 per cent there was direct extension of the primary focus. In 72.2 per cent there was distant metastatic infection. The most common of these infections were superficial abscess and staphylococcic pneumonia.

In all the patients who recovered the infection was focalized into an abscess amenable to surgical treatment.

There were several factors which influenced either the onset or the course of the bacteremia: rupture of the local defense mechanism, wound, trauma, diabetes mellitus, arteriosclerosis, heart disease and cancer.

The virulent staphylococcus contains a type-specific carbohydrate, possesses a capsule and is capable of elaborating toxic substances, which are named according to their properties, such as hemolytic, dermatonecrotic and intravenous lethal factors, leukocidin and coagulase. Some strains are capable of producing a gastrointestinal toxin and fibrinolysin.

The course of the infection in man and that in experimental animals are parallel and can be classed under one of four types: (a) bacteremia without metastatic infection and with rapid death; (b) bacteremia with metastatic infection and death; (c) clearance of bacteremia with focalized metastatic infection and death, and (d) clearance of bacteremia with focalized metastatic infection and recovery.

Recovery of the host apparently depends on the presence of three conditions: (a) active and viable leukocytes and phagocytes; (b) anti-

bacterial antibodies, and (c) antibodies to the toxins, especially to the lethal toxin and to leukocidin.

REPORT OF CASES

Group 1.—Bacteremia; rapid death.

CASE 37.—A man aged 52 was well until five days before admission to the hospital, when he had a chill, which was followed by high fever and pain in the groin. Physical examination showed an extremely ill man with the signs

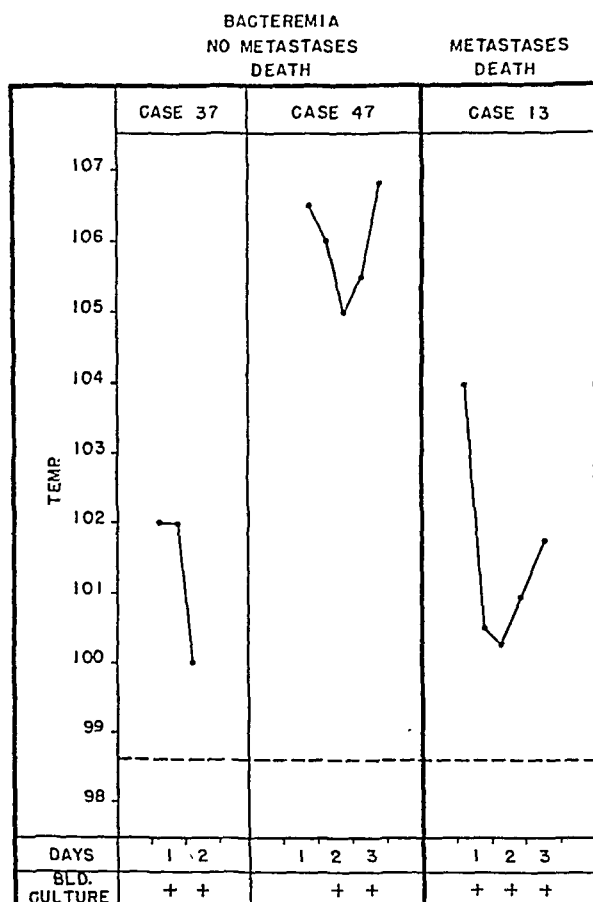


Fig. 3.—Temperature charts of 3 patients with bacteremia caused by *Staph. aureus* whose illness ran a fulminating course.

of bilateral bronchopneumonia. Cultures of the blood were positive for *Staph. aureus* on two successive days. He failed rapidly and died on the seventh day of his illness (fig. 3).

The anatomic diagnoses were: (1) staphylococcic bacteremia, (2) bilateral bronchopneumonia, (3) vegetative endocarditis of the tricuspid valve, (4) embolic nephritis and (5) jaundice.

This case was an instance of sepsis, caused by *Staph. aureus* and lasting only seven days, in which only bronchopneumonia was found on physical examination and the source of the bacteremia was obscure.

Necropsy showed vegetative endocarditis of the tricuspid valve, bilateral bronchopneumonia and pyelitis, with embolic nephritis. It is possible that the endocarditis was secondary to the infection of the renal tract, which was latent, and that the final episode of bacteremia was due to the vegetative endocarditis. In any event, staphylococcic endocarditis is extremely infrequently encountered at necropsy as a feature of rapidly progressing sepsis in which *Staph. aureus* is the causative agent. It is sufficiently common to make one consider it as a possible focus of infection in any patient who has repeatedly positive blood cultures without localizing signs. In the case of acute endocarditis the course of illness may be so rapid that the patient dies before there is destruction of the valves of the heart. In such a case cardiac murmurs are absent.

CASE 47.—A boy aged 8 was well until six days before death, when he became acutely ill with high, irregular fever and pain in the groin. There were no localized signs of infection, but a culture of the blood was positive for staphylococci. Death occurred two days after admission to the hospital (fig. 3).

Necropsy showed miliary abscesses of the myocardium, spleen and pancreas, without any other lesions.

This case was an example of sepsis caused by *Staph. aureus* without an obvious portal of entry and without any signs of localized infection. Death occurred within six days after the onset of symptoms.

CASE 13.—In a man aged 46, who had a carbuncle on the back of the neck, a chill suddenly developed, with a high, remittent fever and signs of bronchopneumonia and stupor. The course of his illness was one of progressive failure, with death occurring six days after the onset of the infection.

Necropsy showed a carbuncle of the neck and multiple abscesses of the brain, liver and kidneys.

This case was an instance of sepsis caused by *Staph. aureus* following an infection of the neck with multiple abscesses in various organs. The course was extremely rapid.

Group 2.—Bacteremia; multiple abscesses; death.

CASE 59.—A girl aged 17 complained of pain in the right leg and fever. Examination showed fever, leukocytosis and signs of osteomyelitis of the right tibia. Culture of the blood was positive for *Staph. aureus* on five occasions. In spite of operative treatment for the osteomyelitis, multiple blood transfusions and administration of staphylococcic antitoxin and sulfanilamide, an abscess of the kidneys and the rectus abdominis muscles developed, and the patient died thirty-two days after the onset of the illness (fig. 4).

This case is an example of osteomyelitis with associated bacteremia and metastatic infection in the kidneys and muscles. The blood was not cleared of organisms in spite of rigorous treatment. Several abscesses were noted at necropsy.

CASE 23.—A boy aged 8 was bitten on the left hand by a white mouse fourteen days before entering the hospital. Within several days the wound became infected, and remittent fever and the constitutional signs of infection

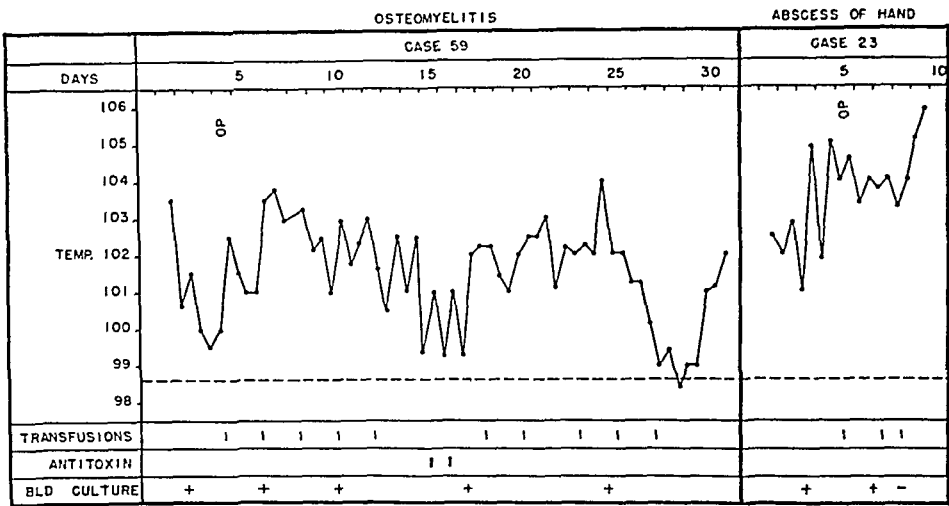


Fig. 4.—Temperature charts of 2 patients in whom bacteremia was followed by metastatic infection and death.

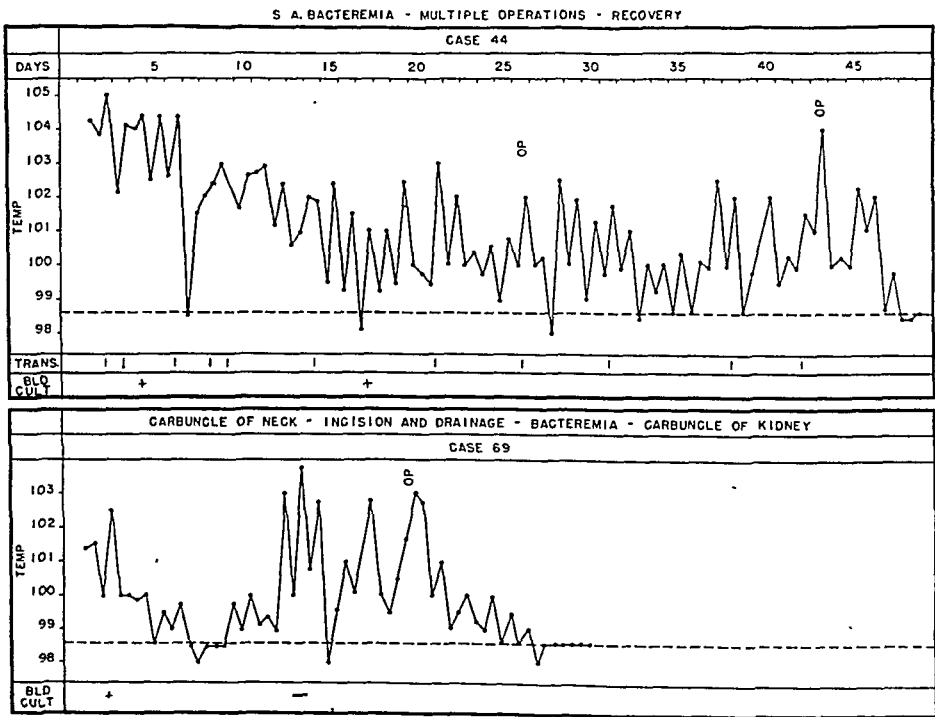


Fig. 5.—Temperature charts of 2 patients in whom bacteremia was followed by clearing of the blood stream, drainage of an abscess and recovery.

developed. At the time of admission there were signs of an infection of the subcutaneous tissues of the left hand and arm, with bacteremia and osteomyelitis of the left ulna and radius. In spite of blood transfusions and surgical drainage

of the abscess and the areas of osteomyelitis, the course was one of progressive failure, and the patient died twenty-three days after the onset of infection (fig. 4).

Group 3.—Bacteremia with clearing of the blood stream; metastases; recovery.

CASE 44.—In a boy aged 14 the signs of acute osteomyelitis of the right tibia developed, with high, remittent fever and bacteremia. Foci of osteomyelitis subsequently developed in the humerus and metatarsal bones, and the blood stream was cleared of bacteria. The foci of osteomyelitis were drained, and the patient recovered after an illness of three hundred and twenty-eight days (fig. 5).

This case illustrates that recovery may occur in a young person with staphylococcic sepsis if it is possible to localize the infection in an abscess which can be drained.

CASE 69.—A woman aged 24 was admitted to the hospital, complaining of chills, fever and generalized prostration. She had been well until two weeks before entry, when a carbuncle developed on the back of the neck. This finally localized in a circumscribed area and was incised two days before her admission. Soon after the incision chills and fever developed. On admission she was acutely ill and showed a draining abscess, caused by *Staph. aureus*, on the back of the neck. There was irregular fever, and a blood culture made on the day of admission was positive for *Staph. aureus*. As the signs of inflammation disappeared from the lesion on the back of the neck, the temperature gradually became lower over a period of nine days and remained normal for two days. Then high, irregular fever began to develop once again, and, within twenty days of admission, there were distinct signs of a perinephritic abscess. This was drained through an incision in the loin. The temperature gradually fell to normal after a period of eight days. Recovery followed, and the patient left the hospital two weeks after operation.

This case was an example of a carbuncle on the neck due to *Staph. aureus* and followed by bacteremia after the abscess was incised. Later a metastatic lesion of the kidney and the perirenal tissues developed, and complete recovery followed only after drainage of the metastatic abscess.

METABOLISM IN ORGANIC HYPERINSULINISM

I. QUANTITATIVE STUDIES OF THE VARIATIONS IN THE RATE OF COMBUSTION OF CARBOHYDRATE PRODUCED BY ALTERATIONS IN THE DIET

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Soon after physicians had come to recognize the characteristic symptoms of insulin hypoglycemia, Harris,¹ in 1924, proposed the concept of endogenous hyperinsulinism. He had noted, in several patients, symptoms similar to those observed after an overdose of insulin and had demonstrated the presence of abnormally low levels of the blood sugar for the duration of such symptoms. He had shown, further, that the symptoms could be relieved promptly by the oral administration of carbohydrate foods. In 1927 Wilder, with others,² in a classic report, presented indisputable evidence that neoplastic pancreatic islet tissue, by producing excessive amounts of substance having the physiologic properties of insulin, caused spontaneous hypoglycemia. It has since been demonstrated repeatedly³ that complete surgical removal of islet cell tumors results almost invariably in disappearance of the hypoglycemic state. Although almost 100 cases have now been reported in which pancreatic islet cell tumors, associated with clinical hyperinsulin-

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3. Howland, G. W.; Campbell, W. R.; Maltby, E. S., and Robinson, W. L.: Dysinsulinism: Convulsions and Coma Due to Islet Cell Tumor of the Pancreas with Operation and Cure, *J. A. M. A.* **93**:674 (Aug. 31) 1929. O'Leary, J. L., and Womack, N.: Histology of Adenoma of Islets of Langerhans, *Arch. Path.* **17**:291 (March) 1934. Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism, *Ann. Surg.* **101**:1299, 1935. Campbell, W. R.; Graham, R. R., and Robinson, W. L.: Islet Cell Tumors of the Pancreas, *Am. J. M. Sc.* **198**:445, 1939.

ism, have been identified at operation or at autopsy, the literature contains surprisingly little quantitative information concerning the abnormal metabolism involved.

The purpose of this report is to record the results of a series of extensive metabolic studies done on a patient with severe organic hyperinsulinism both before and after the surgical removal of multiple islet cell tumors. This first group of studies compares the rate of utilization of carbohydrate in a person with organic hyperinsulinism and that in normal persons under a variety of conditions. It is known, for example, that a short period of restriction of carbohydrate in the diet of the normal person results in a significant decrease in his ability to utilize a standard dose of dextrose.⁴ This is manifested by a prolonged postprandial elevation of the blood sugar, glycosuria, failure to obtain the usual rise of the respiratory quotient and increased catabolism of protein. A similar, but more severe, depression of the ability to metabolize a test dose of dextrose has been shown to occur in starving dogs. This abnormality is completely corrected in three to five days by the daily administration of 50 Gm. of dextrose.⁵ Recent work⁶ indicates that dogs deprived of food for seven days have much less insulin in their pancreas than do well fed dogs. It might thus be concluded that lack of dietary carbohydrate depresses the formation of insulin in the pancreas.

If restriction of dietary carbohydrate failed to induce the usual depression of carbohydrate utilization associated with organic hyperinsulinism but did produce this phenomenon after removal of the abnormal islet tissue, certain hitherto unsettled problems would be clarified: (1) that depression of the rate of utilization of carbohydrate by antecedent restriction of carbohydrate is related to physiologic function of normal pancreatic islet tissue, and (2) that failure of this phenomenon in organic hyperinsulinism indicates an inability of the usual depressing influences to decrease the production of insulin. These and various other quantitative relations are reported herein. We are not aware of any other similarly controlled metabolic studies on patients with organic hyperinsulinism.

4. (a) Sheldon, J. M.; Johnston, M. W., and Newburgh, L. H.: A Quantitative Study of the Oxidation of Glucose in Normal and Diabetic Men, *J. Clin. Investigation* **16**:933, 1937. (b) Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, *Am. J. M. Sc.* **199**:555, 1940. (c) Sweeney, J. S.: Dietary Factors That Influence the Glucose Tolerance Test, *Arch. Int. Med.* **40**:818 (Dec.) 1927.

5. Dann, M., and Chambers, W. H.: Animal Calorimetry: The Metabolism of Glucose Administered to the Fasting Dog, *J. Biol. Chem.* **89**:675, 1930.

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Several preliminary statements are necessary to characterize the conditions of experimentation and the subjects of these investigations. The experimental data were obtained during a period of seven months' continuous hospitalization of a patient with organic hyperinsulinism (preoperative period four months; postoperative period three months). Follow-up studies after discharge have been made at monthly intervals up to the present (three months). The patient, whose condition was misdiagnosed as epilepsy, had been having frequent attacks of convulsions for ten years prior to our studies. Of 182 determinations of blood sugar made during the preoperative period, the results of 55 ranged from 12 to 35 mg. per hundred cubic centimeters; of 86 made in the postoperative period, values for only 3 fell below 75 mg. per hundred cubic centimeters. All 3 were obtained during the course of a dextrose tolerance test, the lowest being 61 mg. per hundred cubic centimeters. At operation, four separate islet cell adenomas were removed from the pancreas. All experiments involving the use of continuous indirect calorimetry were controlled by means of identical experiments on normal subjects who prior to the experiments had been kept under the same conditions as those imposed on the abnormal subject. Additional control of the preoperative experiments, the data from which disclosed grossly abnormal metabolism, was obtained by repeating the experiments after operation. A detailed summary of the clinical data and of the operative and pathologic observations follows.

REPORT OF A CASE

A 59 year old white woman, a widow, had been in excellent health until January 1930 (almost ten years before her admission to the hospital), when "attacks" began. While in a trolley car on her way home from work at 6:30 p. m., she was roused at the end of the line by the conductor, who told her that she had been staring straight ahead and jerking her right arm. She managed to change cars and arrived home in a dazed state, perspiring profusely and having only a vague recollection of what had happened since she had left her office. She was ravenously hungry and recalled that she had had no breakfast and only a light lunch. She ate heartily and within fifteen minutes was again perfectly well. From then on she noticed that the omission, or sometimes the delay, of a meal would bring on a "nervous spell." Throughout the ten year period attacks came at the average rate of one or two a week, with increasing severity but not increasing frequency. For the first seven years most of the attacks occurred between 5:00 and 6:00 p. m., but more recently they came almost always between 10:00 a. m. and noon. There was never an attack during the night or before breakfast.

The typical attack was characterized by an "aura" of epigastric discomfort and numbness, first of the lips and then of the extremities. There followed a peculiar fixed and facetious expression of the face, complete change in personality, diplopia, beginning confusion and disorientation associated with jerking movements of all extremities and muscles of the jaw, complete loss of consciousness and generalized

tonic and clonic convulsions. Attacks continued for ten to sixty minutes. The patient found that an attack could be aborted by the ingestion of food. Her weight increased from 150 to 170 pounds (68 to 77.1 Kg.) in the year previous to admission to the hospital. For several months, on arising in the morning, she experienced an occipital headache which disappeared after breakfast. A diagnosis of epilepsy was made.

On Nov. 4, 1939 she entered the University Hospital for study. Except for obesity, the physical examination revealed nothing abnormal. She was given a general diet, and two days later at 11:45 a. m. a typical attack was observed. The blood sugar level during the attack was 24 mg. per hundred cubic centimeters.

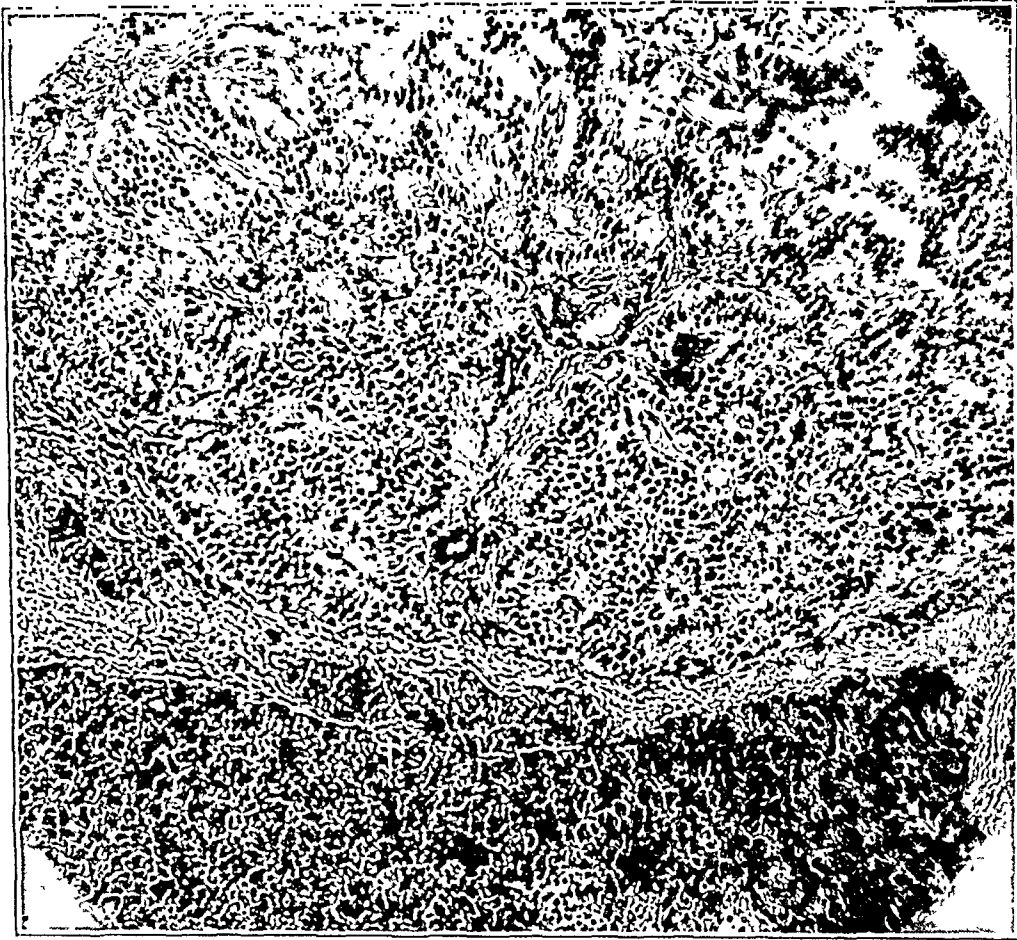


Fig. 1.—Section through the periphery of an islet cell adenoma.

The attack was quickly terminated by the intravenous administration of 5 Gm. of dextrose. After a five day period of standard dietary preparation^{4b} the dextrose tolerance test gave the following results: fasting, 47 mg. per hundred cubic centimeters; one hour, 95 mg.; two hours, 47 mg.; three hours, 45 mg.; four hours, 43 mg., and five hours, 56 mg.

Hepatic function was normal, as indicated by bromsulphalein, hippuric acid and galactose tolerance tests. Levels of blood bilirubin, urinary urobilinogen and serum proteins were normal. A cholecystogram showed faint visualization, with probable stone.

Roentgenograms of the skull showed a normal pituitary fossa. The visual fields were normal. The basal metabolic rate was -7 per cent. Results of the sodium restriction test⁷ revealed no evidence of decreased adrenal cortical function.

While the patient was on a diet low in carbohydrate, her fasting blood sugar values ranged from 21 to 37 mg. per hundred cubic centimeters. Except for mild headache, however, there were no attacks before breakfast. Typical attacks came on daily with clocklike regularity, between 11:15 a. m. and noon, with blood sugar values between 14 and 35 mg. per hundred cubic centimeters. A diagnosis of organic hyperinsulinism was made, and the metabolic studies were begun (see "Results").

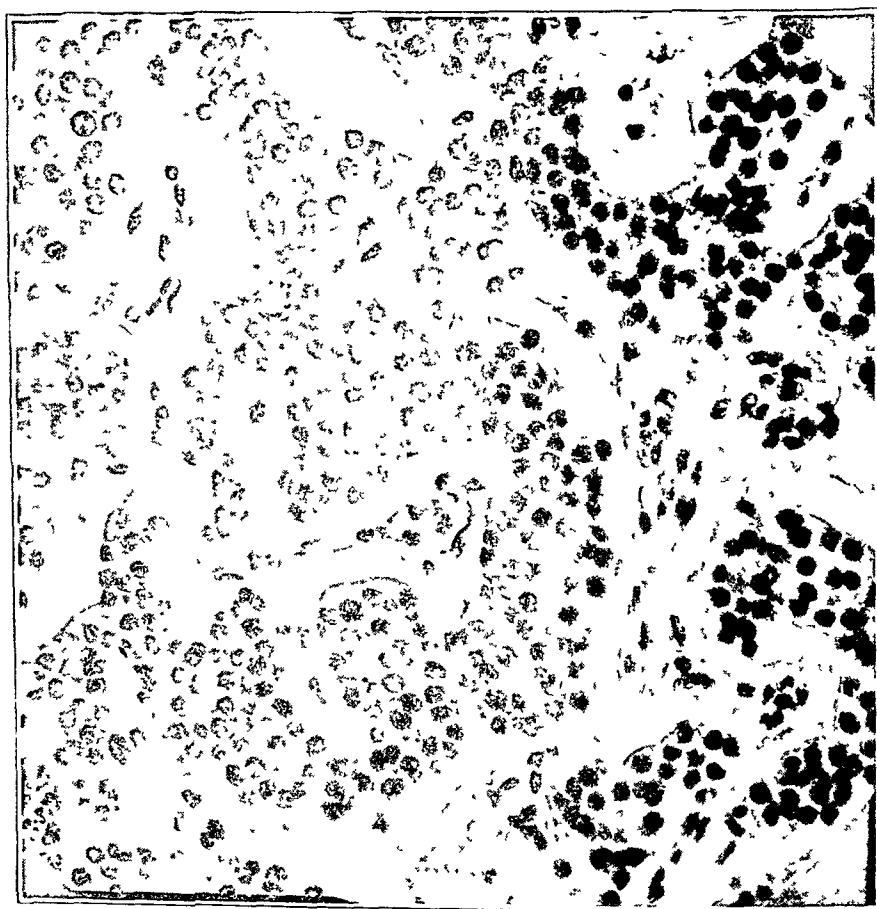


Fig. 2.—Greater magnification, showing cellular detail, of a portion of section in figure 1.

On Feb. 24, 1940 exploratory laparotomy was done by Dr. F. A. Coller. At the junction of the distal and the middle third of the tail of the pancreas a firm nodular area was felt. This area, with all the pancreas distal to it, was resected and was found to contain, deep in its substance, three separate and well encapsulated adenomas, varying from 0.5 to 1.5 cm in diameter (figs 1 and 2). Sections revealed another adenoma of microscopic dimensions in the same region. In the pancreatic tissue itself were areas in which the islands of Langerhans were

7. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentration of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, *J. A. M. A.* **111**:117 (July 9) 1938.

markedly hypertrophic and hyperplastic (fig. 3). A specimen of the liver was taken for biopsy and for determination of glycogen content. Microscopically it appeared normal. It was noted, however, that there was a marked finely vacuolar state of the liver cells, which was not lipoidal in nature (fig. 4). This was interpreted as indicating a high content of glycogen. Chemical analysis revealed a glycogen content of 5.5 per cent. The gallbladder, which was thickened and contained several pea-sized stones, was removed.

Postoperatively a period of temporary hyperglycemia, glycosuria and ketonuria was observed. Over a period of two weeks and without the aid of exogenous insulin, the level of fasting blood sugar gradually became stabilized in the normal

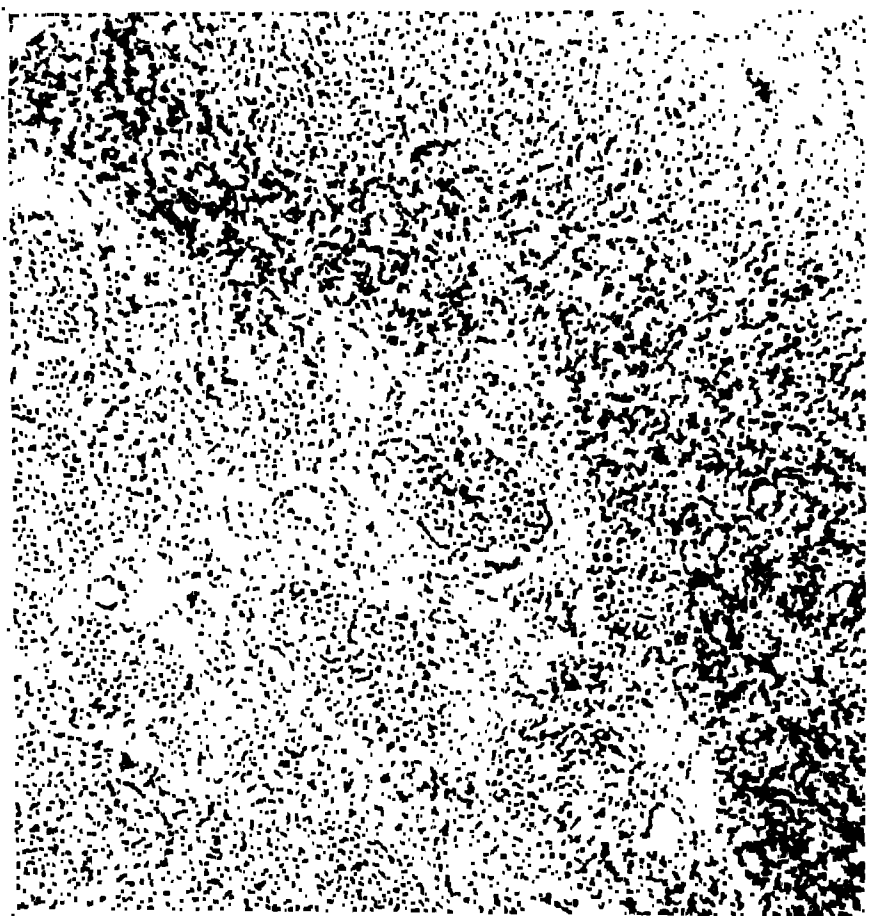


Fig. 3.—Numerous hypertrophic and hyperplastic islands of Langerhans.

range and subsequently remained there, regardless of the diet (see "Results"). Over the six months' postoperative period there has been no suggestion of hypoglycemia. The patient has returned to her daily household duties and has maintained excellent health.

METHODS OF INVESTIGATION

A respiration chamber⁸ employing the principle of continuous indirect calorimetry by the open circuit method was used to obtain the data on metabolism.

8. Newburgh, L. H.; Johnston, M. W.; Wiley, F. H.; Sheldon, J. M., and Murrill, W. A.: A Respiratory Chamber for Use with Human Subjects, *J. Nutrition* **13**:193, 1937.

Frequent checks of the chamber by means of the combustion of alcohol demonstrated that the method is capable of determining over 99 per cent of the gaseous exchange. Each collection of respired gases from the patient and from the control subjects covered a continuous four hour period (8:00 a. m. to noon). On the evening preceding an experiment the subject was put to bed in the chamber. The chamber was sealed and the entire mechanism was set in operation. At 8:00 a. m. the next morning the turning of two stopcocks was all that was necessary to begin the collection of a continuous sample of chamber air. Analysis of gases was done by the technic of Carpenter.⁹ Carefully weighed, constant diets were used throughout all experiments. Whenever a change in the composition of the diet was

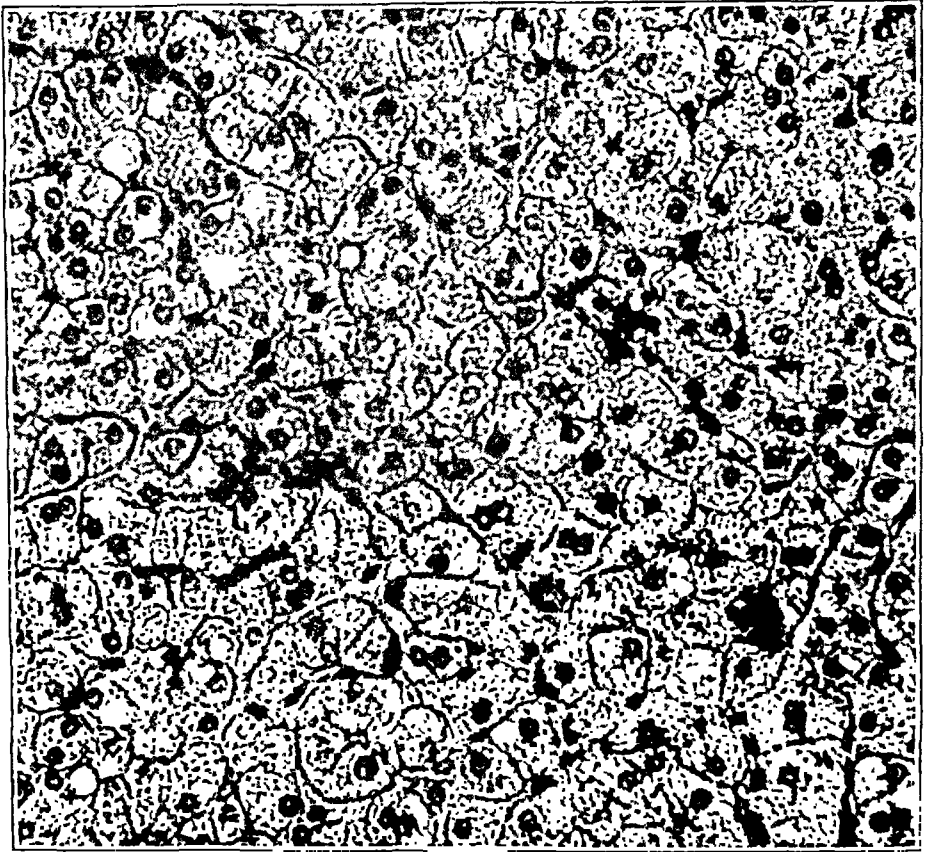


Fig. 4.—Biopsy section of the liver. Note the marked nonlipoidal intracellular granularity. The glycogen content was 5.5 mg. per hundred grams.

instituted, a period of at least five days was allowed for physiologic adjustment before the next experiment was carried out. Data on gaseous exchange were calculated in the standard way.¹⁰ Blood sugar was determined by the Benedict

9. Carpenter, T. M.: Ein Apparat zur Analyse von Gasen aus Respirationskammern für Menschen und Tiere, in Abderhalden, E.: *Handbuch der biologischen Arbeitsmethoden*, Berlin, Urban & Schwarzenberg, 1937, pt. 4, sect. 13, p. 593.

10. Lusk, G.: *The Elements of the Science of Nutrition*, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 61.

method¹¹ and urinary nitrogen by the Kjeldahl method. Liver glycogen was determined by the method of Good, Kramer and Somogyi,¹² the specimen of liver having been frozen by solid carbon dioxide immediately on its removal from the body.

RESULTS

Convulsive Seizures.—In the preoperative period a total of fifty convulsive attacks were observed (fig. 5). Seventy-four per cent of them occurred between 11:15 a. m. and 12:50 p. m. and 14 per cent between 4:00 and 5:30 p. m. Only two attacks occurred before breakfast, although the level of blood sugar was frequently lower then than at 11:30 a. m., when a convulsion usually took place. Attacks occurred

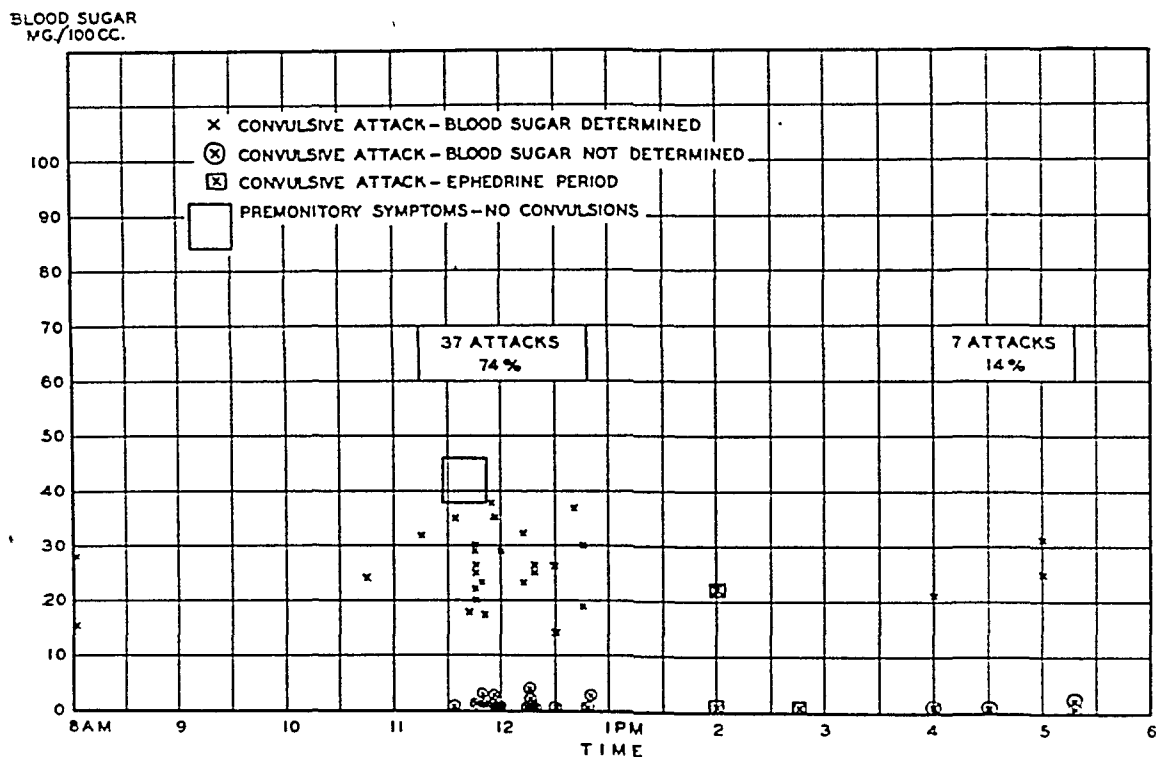


Fig. 5.—Time incidence of the fifty convulsive attacks observed.

at levels of blood sugar ranging from 13 to 38 mg. per hundred cubic centimeters. When convulsions did not appear at the expected hour, premonitory symptoms (numbness of the lips, hands and feet; visual disturbances; trembling, etc.) were extremely frequent between 11:25 and 11:50 a. m., at blood sugar levels of 38 to 47 mg. per hundred cubic centimeters.

11. Benedict, S. R.: The Analysis of Whole Blood: II. The Determination of Sugar and of Saccharoids (Non-Fermentable Copper Reducing Substances), J. Biol. Chem. **92**:141, 1931.

12. Good, C. A.; Kramer, H., and Somogyi, M.: The Determination of Glycogen, J. Biol. Chem. **100**:485, 1933.

Indirect Calorimetry.—The table summarizes the data on the patient and on the control subjects obtained from four hour periods of continuous indirect calorimetry. When prepared for five days with a diet yielding maintenance calories and containing 300 Gm. of carbohydrate and 80 Gm. of protein and when given a test dose of 60 Gm. of dextrose in the chamber on the morning of the experiment, the patient derived 97.6 per cent of her nonprotein calories from the combustion of carbohydrate and only 2.4 per cent from the oxidation of fat. Under the same conditions the controls obtained only 50 to 60 per cent of their nonprotein calories from carbohydrate and 40 to 50 per cent from fat. Thus, under these conditions, the patient gave evidence of tremendous overcombustion of carbohydrate at the expense of fat. Fifty-three days after operation the results for the patient fell into the normal range.

The conditions of the second experiment were essentially the same, the only alteration having been a change in the preparatory diet. The carbohydrate content of the preparatory diet was reduced from 300 to 100 Gm., and an isocaloric amount of fat was added. The protein content remained constant. The test dose of dextrose (60 Gm.) was the same. Note that reduction of the carbohydrate content of the preparatory diet of the normal subjects reduced the rate of combustion of carbohydrate, despite the fact that the same quantity of dextrose was presented for combustion in the form of the test dose. The patient, under these conditions, demonstrated a marked reduction in the rate of oxidation of carbohydrate. As compared with the normal level of carbohydrate combustion under these conditions, however, there was still evidence of great overcombustion of carbohydrate. Sixty-five days after operation the rate of carbohydrate oxidation appeared to be slightly subnormal. Fifteen days later the metabolic mixture was normal.

In the third experiment, the preparatory diet was the same as that used for the second (carbohydrate, 100 Gm.; protein, 80 Gm., and maintenance calories). The only variation was the elimination of the test dose of dextrose. The subjects drank an equivalent volume of water at the beginning of the four hour period in place of the usual solution of dextrose. Thus, by a comparison of results of the second and third experiment we obtained a measure of (1) the rate of postabsorptive combustion of carbohydrate when the preparatory diet had been moderately low in carbohydrate and (2) the effect per se of the ingestion of 60 Gm. of dextrose on combustion of carbohydrate. It is seen that under these conditions of dietary preparation the rate of postabsorptive combustion of carbohydrate by the patient was reduced to the normal level. The comparison of results, however, brings out a significant fact. Although under the conditions of experiment 2 both the patient and the controls oxidized carbohydrate at the same rate in the postabsorptive

Combustion of Carbohydrate, Fat and Protein
Four Hour Test Periods in Respiration Chamber

Experi- ment No.	Subject	Preparatory Diet (5 Days), with Maintenance		Post Chamber; Dextrose, Gm.	Total Res- piratory Quotient	Non- pro- tein Res- piratory Quotient	Total Heat Produced, Calories	Heat Produced, Protein Calories	Heat Produced, Non- protein Calories	Sources of Nonprotein Calories, Percentage		Comment
		Carbo- hydrate, Gm.	Protein, Gm.							Carbo- hydrate	Fat	
1	Patient	300	80	60	0.956	0.992	207	17	230	97.6	2.4	Before operation
	Control	300	80	60	0.848	0.867	291	15	246	53.1	46.9	
	Control	300	80	60	0.863	0.876	282	15	237	59.5	11.5	
	Control	300	80	60	0.874	0.887	312	40	293	63.1	36.9	
	Control	300	80	60	0.841	0.846	378	37	341	49.3	50.7	53 days after operation
2	Patient	300	80	60	0.865	0.872	296	28	268	58.2	11.8	Before operation
	Patient	100	80	60	0.884	0.901	267	42	225	67.8	32.2	Before operation
	Control	100	80	60	0.820	0.824	327	53	274	11.7	58.3	
	Control	100	80	60	0.832	0.838	310	52	258	16.5	53.5	
	Patient	100	80	60	0.833	0.863	268	35	233	34.5	65.5	65 days after operation
3	Patient	100	80	60	0.826	0.830	274	35	239	43.8	56.2	80 days after operation
	Patient	100	80	0	0.780	0.776	253	39	214	24.9	75.1	Before operation
	Patient	100	80	0	0.794	0.792	257	41	216	39.6	60.4	Before operation
	Control	100	80	0	0.782	0.778	328	56	272	25.6	74.4	
	Control	100	80	0	0.792	0.790	336	48	288	29.9	70.1	
4	Control	100	80	0	0.791	0.790	335	48	287	29.9	70.1	
	Patient	300	80	0	0.868	0.882	250	39	211	61.5	38.5	Before operation

state, the ingestion of 60 Gm. of dextrose afforded in the patient a much greater stimulus for the combustion of carbohydrate than it did in the controls.

Two other observations must be mentioned here since they support certain conclusions. 1. Despite the fact that a low carbohydrate preparatory diet reduced the rate of postabsorptive combustion of carbohydrate by the patient to the level exhibited by the normal subjects, the blood sugar level of the patient continued to fall slowly in the four hour period without food. The blood sugar level of the controls, on the other hand, remained relatively constant. 2. The rate of postabsorptive combustion of carbohydrate by the patient when she had been previously

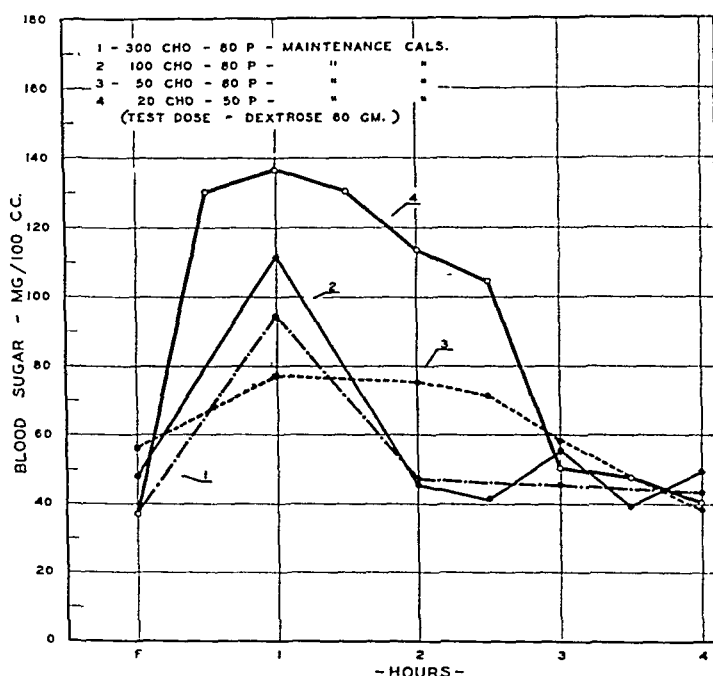


Fig. 6.—Effect of previous diet on the dextrose tolerance curve in a case of organic hyperinsulinism before surgical removal of islet cell tumors.

prepared with a higher carbohydrate diet (table, experiment 4) was as great as the rate in normal subjects prepared in the same way but given in addition 60 Gm. of dextrose (group 1). Stated differently, under conditions of high carbohydrate preparation the postabsorptive rate of carbohydrate combustion in the patient was at least as rapid as the postprandial rate in normal persons.

Dextrose Tolerance Curves.—Another experiment, dealing with the effect of variations in the carbohydrate content of the preparatory diet on the blood sugar time curve after the ingestion of dextrose, was done for the following reasons: 1. It has been shown repeatedly that manipu-

lation of the antecedent diet of a normal person produces remarkable changes in the shape of the dextrose tolerance curve. 2. All types of dextrose tolerance curves have been reported in cases of proved organic hyperinsulinism. We believe much of this confusion to be due to the lack of a standardized preparatory diet.

Figure 6 shows that the type of curve obtained in a case of organic hyperinsulinism is influenced by the composition of the antecedent diet. It should be pointed out that these differences were obtained after relatively short periods (five days) of preparation with the various diets;

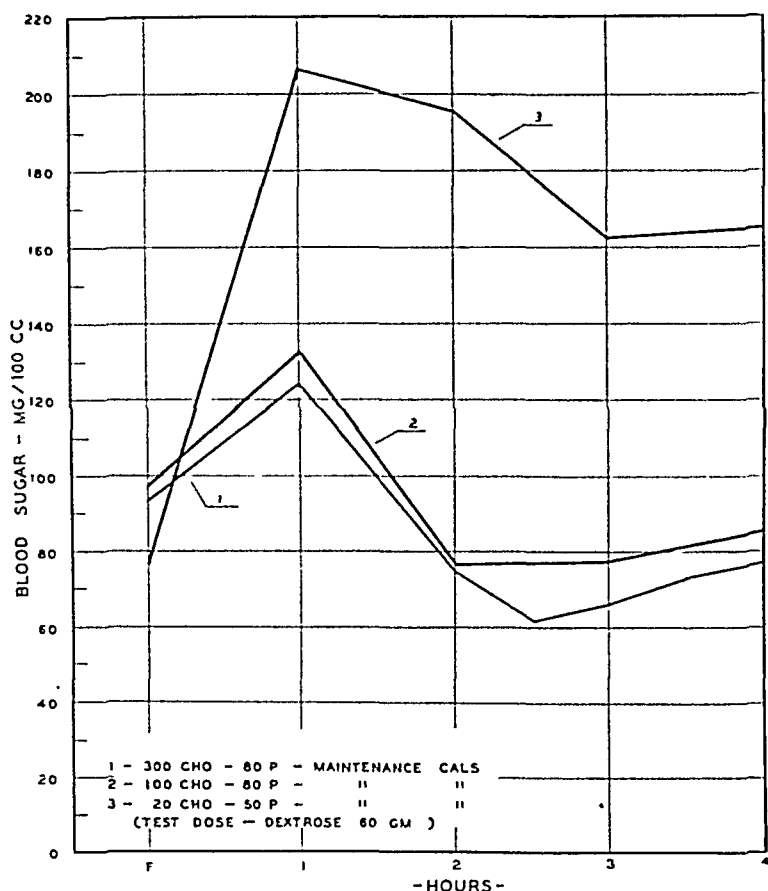


Fig. 7.—Effect of previous diet on the dextrose tolerance curve in a case of organic hyperinsulinism six months after surgical removal of islet cell tumors.

longer periods would be expected to produce even wider variations. Figure 7 shows the results of the same experiments made on the same patient six months after operation (the experiment represented by curve 3, figure 6, was not repeated). It may be seen that qualitatively the responses are the same. The degree of change, however, produced by a short period of sharp restriction of carbohydrate is greater after the normal metabolism of carbohydrate has been restored.

Observations During the Early Postoperative Period.—In figure 8 are shown data obtained in the immediate preoperative and postoperative

periods. For ten days before operation the level of the fasting blood sugar ranged from 22 to 47 mg. per hundred cubic centimeters. Twenty-four hours after operation the fasting blood sugar level was 320 mg. per hundred cubic centimeters and was accompanied by heavy glycosuria and ketonuria. No exogenous insulin was given. The ketonuria disappeared in twenty-four hours, but the glycosuria persisted for five days. The level of the fasting blood sugar fell slowly, reaching 100 mg. per hundred cubic centimeters on the seventh postoperative day. For three weeks it remained close to 100 mg. and then stabilized between 90 and 100 mg. per hundred cubic centimeters, where it has remained for

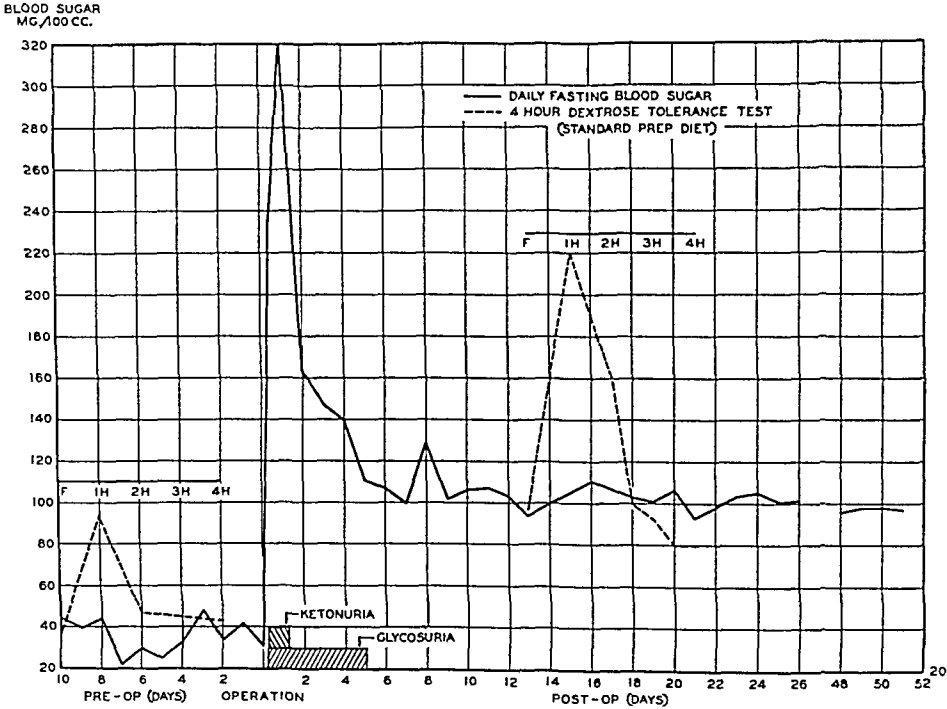


Fig. 8.—Preoperative and postoperative fasting blood sugar levels and dextrose tolerance curves in a case of organic hyperinsulinism.

the past four months. The broken lines compare a preoperative dextrose tolerance curve with an early postoperative one, both having been preceded for five days by the standard preparatory diet.

COMMENT

Organic hyperinsulinism represents only one of a great many causes of spontaneous hypoglycemia. In classifying, from the point of view of clinical behavior, the various etiologic types of spontaneous hypoglycemia one of us ¹³ divided them into two broad groups, namely, the

13. Conn, J. W.: Spontaneous Hypoglycemia: Classification and Principles of Treatment, in Therapeutics of Infancy and Childhood, New York, Paul B. Hoeber, Inc., to be published.

stimulative hypoglycemias and the fasting hypoglycemias. The best example of the stimulative type is that condition designated as functional hyperinsulinism, in which a precipitous fall of the blood sugar to hypoglycemic levels follows the ingestion of large amounts of carbohydrate. The level of the fasting blood sugar, however, remains normal even when dietary carbohydrate is restricted. The episodes of transient postprandial hypoglycemia are controlled by reducing the carbohydrate content of the diet. The fasting type of spontaneous hypoglycemia is well illustrated in cases of certain kinds of severe hepatic disease in which restriction of dietary carbohydrate produces a low level of the fasting blood sugar. A diet high in carbohydrate controls the fasting hypoglycemia.

Organic hyperinsulinism appears to include both of these types. A low level of the fasting blood sugar is always found, and restriction of the carbohydrate of the diet depresses it further. In this sense the condition may be classified as a fasting hypoglycemia. At the same time, however, a stimulative effect is seen in the fact that two to four hours after a meal the level of the blood sugar is frequently far below that observed in the postabsorptive state. It is thus noteworthy (fig. 5) that of fifty hypoglycemic attacks observed in the preoperative period, 74 per cent occurred in the forenoon and 14 per cent in the late afternoon. Hypoglycemia, usually asymptomatic, was always present before breakfast, but the blood sugar level was frequently lower four hours after breakfast. An active and rapid reduction of the blood sugar level in the postprandial period is, therefore, evident. The results of the studies on gaseous exchange (table) demonstrated overcombustion of carbohydrate following a test dose of dextrose, regardless of the antecedent diet. We regard these observations as evidence of an excessive stimulation by the ingestion of carbohydrate of those mechanisms involved in the rapid removal of sugar from the blood. Since all such evidence disappeared on the removal of the islet cell tumors, it seems fair to conclude that the stimulative effect had been on the islet tissue and had resulted in an excessive secretion of insulin.

In the postabsorptive state, the gradual fall of the blood sugar must be due to one of the following elements or to a combination of them; (1) abnormal withdrawal of blood sugar for storage as glycogen; (2) abnormal withdrawal of blood sugar for combustion, and (3) insufficient supply of sugar from the liver to the blood to meet the requirements of utilization of sugar. The finding of 5.5 per cent glycogen in the liver at operation when the level of fasting blood sugar on the same morning was 24 mg. per hundred cubic centimeters suggested that abnormal retention of hepatic glycogen was a factor. The demonstration that on a normal diet the rate of combustion of carbohydrate by the patient in

the postabsorptive state was markedly increased (table, experiment 4) indicates that this mechanism, too, was at work reducing the level of the fasting blood sugar. It appears, then, that the fasting hypoglycemia, obviously the result of too much insulin, is associated with both abnormal inhibition of hepatic glycogenolysis and excessive combustion of sugar.

The results obtained by indirect calorimetry¹⁴ may be summarized in the following way: As compared with normal persons, the patient with organic hyperinsulinism who is eating an average diet derives a much greater percentage of total heat from the combustion of carbohydrate, in the postabsorptive as well as in the postprandial state. This appears to indicate a continuously excessive secretion of insulin. Limitation of carbohydrate in the antecedent diet reduces the postabsorptive rate of combustion of carbohydrate to the same level as that exhibited by normal subjects under the same conditions. But, even under these circumstances, the ingestion of dextrose results in much greater combustion of carbohydrate in a person with organic hyperinsulinism than in a normal person. This indicates an excessive responsiveness of the insulin-forming mechanism to the normal stimulus. Removal of islet cell tumors results in the restoration of the normal rate of combustion of carbohydrate under all the conditions just mentioned.

The demonstration that such a patient derives a significantly greater percentage of his total heat from the combustion of carbohydrate is not surprising. But the observation that a diet restricted in carbohydrate reduces the postabsorptive rate of carbohydrate oxidation to the normal

14. Several points regarding the information obtained by continuous indirect calorimetry are worthy of emphasis. Wilder and associates,² in their study of the first proved case of organic hyperinsulinism, using the technic of periodic sampling of respired gases, observed individual respiratory quotients as high as 1.06 after the ingestion of 100 Gm. of dextrose. Others (Liu, S. H.; Loucks, H. H.; Chou, S. K., and Chen, K. C.: Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism: Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, *J. Clin. Investigation* **15**:249, 1936), using the same methods, have reported respiratory quotients approaching unity in similar cases after the administration of dextrose. Respiratory quotients which approach unity for a short period after the ingestion of dextrose can be demonstrated consistently in normal persons, the height of the respiratory quotient being a function of the antecedent diet, the amount of dextrose administered, the time of collection of gases after ingestion of dextrose and several other variables. Hence, a calculation of the total combustion of carbohydrate over a given period is not valid unless the respiratory quotient of the total respiratory exchange for the period is obtained. Continuous indirect calorimetry meets this requirement. The use of long periods of standard dietary preparation and the inclusion of normal subjects studied under the same conditions allow a quantitative comparison of carbohydrate combustion.

level requires further elucidation. At first glance, one might conclude that under conditions of low carbohydrate feeding the rate of post-absorptive liberation of insulin is reduced to the normal level. It is well known clinically, however, and it was demonstrated again in this patient, that in dealing with organic hyperinsulinism restriction of dietary carbohydrate leads to intense postabsorptive hypoglycemia. Thus, even though the combustion of sugar is not excessive, the blood sugar continues to fall to hypoglycemic levels. How, then, can one reconcile these two apparently conflicting sets of evidence?

The analysis of a specific experiment brings out the problem more clearly. During a five day period of low carbohydrate preparation for a respiration experiment the fasting blood sugar level (8:00 a. m.) averaged 52 mg. per hundred cubic centimeters (range, 45 to 65 mg. per hundred cubic centimeters). On the sixth morning a four hour chamber study of oxidation with the patient in the fasting state was made (8:00 a. m. to noon). The blood sugar at noon was 38 mg. per hundred cubic centimeters. There was, therefore, a gradual fall of the blood sugar, despite the fact that the rate of combustion of carbohydrate during the period was normal (table). Under these conditions, a mechanism other than overcombustion of carbohydrate was responsible for the gradual fall of the blood sugar. It seems likely that the rate of hepatic glycogenolysis was too slow to supply to the blood that amount of dextrose necessary to satisfy the normal rate of utilization by the tissues. The large amount of glycogen found in liver by us and by others supports this assumption. It appears, then, that in cases of organic hyperinsulinism restriction of dietary carbohydrate may reduce the rate of postabsorptive combustion of carbohydrate to the normal level but that evidence of excessive insulin activity is still manifested by an abnormal inhibition of hepatic glycogenolysis and resultant hypoglycemia. In this condition, therefore, the secretion of excessive amounts of insulin cannot be brought under control by the institution of a diet low in carbohydrate. The abnormal islet tissue seems to have acquired at least partial independence of the usual depressing influences.

The diagnostic significance of the dextrose tolerance test in cases of organic hyperinsulinism has been questioned because all types of curves have been obtained in proved cases. All types of curves can be produced in normal people,¹⁵ as well as in those with organic hyperinsulinism (fig. 6), if one varies the amount of carbohydrate in the antecedent diet. Since in the past no attempt has been made to control the antecedent diet, it is not surprising that wide variations have occurred. We suggest that the use of a standard preparatory diet ^{4b} will result in much more comparable and reproducible results.

15. Conn.^{4b} Sweeney.^{4c}

CONCLUSIONS

When the composition of the diet is average with respect to carbohydrate, protein and fat, there is associated with organic hyperinsulinism tremendous overcombustion of carbohydrate, both in the postprándial and in the postabsorptive state. Since the normal rate of combustion of carbohydrate is restored by the removal of islet cell tumors, we regard these observations as evidence of a continuously excessive secretion of insulin.

A diet low in carbohydrate depresses the rate of combustion of a standard test dose of dextrose. As compared with the normal rate under the same conditions, however, the rate of combustion of carbohydrate in organic hyperinsulinism is still greatly increased.

In persons with organic hyperinsulinism a diet low in carbohydrate depresses the postabsorptive rate of carbohydrate oxidation to the same level as that exhibited by normal persons under the same conditions. Nevertheless, the fasting blood sugar of the former continues to fall to hypoglycemic levels while that of the latter does not.

Excessive inhibition of hepatic glycogenolysis accounts for the postabsorptive hypoglycemia occurring when the rate of combustion of carbohydrate has been depressed to the normal level by low carbohydrate feeding. The association of postabsorptive hypoglycemia with a large amount of glycogen in the liver supports this contention.

Under all conditions studied, evidence of excessive liberation of insulin has been encountered. While the rate of excessive production of insulin appears to be influenced to some degree by variations in the carbohydrate content of the diet, the liberation of insulin cannot be sufficiently depressed by low carbohydrate feeding to prevent hypoglycemia.

Variations in the type of dextrose tolerance curve produced in persons with organic hyperinsulinism by changes in the antecedent diet are qualitatively similar to variations in those produced in normal persons, but the degree of variation is less in the former. A standard preparatory diet results in much more comparable and reproducible curves.

BLOOD SUGAR IN A CASE OF COMPLETE HYPOPHYSECTOMY

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AND

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In this communication we shall show primarily that total removal of the pituitary body lowers the fasting blood sugar to a hypoglycemic level without shock and gives a delayed sugar tolerance curve, which may be a plateau at times. Furthermore, we shall show that the blood sugar level is not wholly dependent on the presence of this gland and that apparently the gland has not complete control over any vital function.

Detailed reports of the surgical procedures employed by the neurosurgeons in the removal of a pituitary tumor and the inadvertent complete removal of the hypophysis are presented with the purpose of proving our contention that no pituitary tissue remained in this case.

Our studies were considerably limited by the patient's extreme irritability and his hypersensitiveness to pain. A number of tests had to be interrupted because of the intense mental and physical reactions incurred.

REPORT OF A CASE

A. S., a 33 year old truck driver, was admitted to the New York City Hospital on April 15, 1937, having been transferred from Bellevue Hospital. His history up to about Jan. 1, 1935 was of no significance. At that time he noticed increasingly severe headaches and failing vision. He was admitted to a local hospital in April 1935, at which time a complete study showed evidence of a tumor of the pituitary body.

On March 14, 1935 incision and elevation of a bone flap, with an attempt at enucleation of the tumor, were carried out. The operative report was as follows: "Beneath the chiasm, and apparently pushing it upward, was a slightly reddish tumor, approximately 2 cm. in diameter, resting within the pituitary fossa. Incision into the visible portion of the tumor was made, and curettement was then done with a pituitary spoon; a considerable amount of exceedingly soft tissue was recovered in small fragments. Eventually a cavity was formed in the tumor mass, large enough to admit two full-sized cotton pledgets. It was deemed wise to discontinue further surgical attempts at ablation and to depend on roentgen therapy."

From the Second Medical Division, New York City Hospital, Department of Hospitals of New York City; service of Dr. John Carroll.

On April 10 the patient returned to the operating room for reelevation of the bone flap and removal of a meningioma of the sella turcica. The operative report read as follows: "The left optic nerve and the left half of the optic chiasm were visible, as was the opening made into the capsule of the tumor underneath the optic chiasm and leading down into the sella, presumably into a cavity within the tumor. The right half of the optic chiasm and the right optic nerve and part of the optic tract lay partly underneath this tumor mass and partly enclosed within it, so that the left end of the chiasm lay superior to the tumor while the right end lay inferior to it. The tumor was removed bit by bit from these nerves until finally they were exposed in toto, the chiasm being badly damaged. It was then possible to free the tumor down to the sella. A flat blade endothermy tip was pushed within the sella and the coagulation current turned on. Tissue thus treated appeared to shrink under the eye. The capsule of the tumor actually pulled away from the walls of the sella, leaving them free and glistening. By means of sytemic coagulation, traction and blunt and sharp dissection, it was finally possible to remove all the tumor from the pituitary fossa, leaving the floor of the fossa smooth and glistening. The actual attachment of the tumor was never determined with certainty, but was probably the tuberculum of the sella. This region was thoroughly cauterized to prevent any local recurrences."

The report of the microscopic examination of the material removed, stated: "The tissue is composed chiefly of epithelial cells, polyhedral and closely packed, with a suggestion of arrangement in columns; the nuclei are compact and the fairly abundant cytoplasm varies from basophilic to pituitary gland cells." A second report mentioned "fibroblastic proliferation with calcific deposits and meningeal hyperplasia, possibly meningioma."

Recovery was uneventful; headaches were relieved, and vision was improved. However, abdominal cramps developed, and the patient was admitted to Bellevue Hospital on Jan. 24, 1937.

On April 15, 1937, when he was transferred to New York City Hospital from Bellevue Hospital, he gave the appearance of a prematurely aged, extremely emaciated man, with fine dry skin, high-pitched voice and feminine distribution of hair. Examination revealed severe abdominal cramps and failing vision. The fundi showed second degree atrophy of the optic nerves and bilateral hemianopia, with loss of visual acuity. There was marked hyperesthesia to touch over the abdomen; no mass was palpable. The blood pressure was 100 systolic and 68 diastolic.

The course of his illness at the City Hospital has been stationary. Treatment has been based on substitution and on symptomatic needs. During the greater part of his stay he has received 6 grains (0.39 Gm.) of whole pituitary and 2 grains (0.13 Gm.) of thyroid daily.

On examination on Oct. 1, 1940, at which time he was a bed patient, he was undernourished and constantly cried out as if in distress. There was rotary nystagmus of both eyes; the disks were barely visible but were normal, and there was poor vision in the right eye, with practically complete blindness in the left. The right arm and hand and both legs were contracted. There were atrophic changes of the skin of the legs and feet, with ulcers. He suffered severely with hyperesthesia and hyperalgesia over the whole body. So extreme was his condition that we hesitated to carry on too exacting an examination.

Roentgenograms of the long bones yielded the following information: "The proximal half of the right radius shows destruction of the cortex along the interosseous border. The bone has an irregular appearance, the result of an osteoid

reaction. The cortex is defined and shows localized areas of thinning and thickening throughout the roentgenograms. The bones forming the right knee joint and the right ankle have undergone decalcification secondary to disuse. The left knee and ankle show similar changes. The head of the left femur is partially destroyed."

The laboratory findings during the patient's stay in the hospital were as follows: urine, essentially normal; Wassermann reaction, negative; nonprotein nitrogen, 27 to 29 mg. per hundred cubic centimeters; icteric index, 6; basal metabolic rate, —7 to —29 per cent; blood chlorides, 353 to 512 mg. per hundred cubic centimeters; blood phosphates, 2.2 to 3.3 mg. per hundred cubic centimeters; blood urea nitrogen, 14.9 mg. per hundred cubic centimeters, and blood cholesterol, 138 to 266 mg. per hundred cubic centimeters. Electrocardiograms were essentially normal. An average blood count revealed 4,000,000 red cells and 7,200 white cells, with a normal differential count; the hemoglobin content was 11 Gm. per hundred cubic centimeters.

The fasting blood sugar on admission was 80 mg. per hundred cubic centimeters. Another determination a little later gave a value of 45 mg. A sugar tolerance test made on Oct. 13, 1938 yielded the following data: fasting, 34 mg.; one-half hour, 65 mg.; one hour, 98 mg.; two hours, 118 mg., and three hours, 34 mg. On June 28, 1939 samples of blood were taken one hour before and one hour after eating, and the sugar content was reported as 66 and 69 mg., respectively, per hundred cubic centimeters. On April 4, 1940 another sugar tolerance test gave the following results: 66, 111, 125, 111 and 108 mg. On Aug. 8, 1940 we began another test but were forced to discontinue it before it was completed. The fasting, half-hour and one hour values were 46, 70 and 76 mg., respectively.

COMMENT

We believe that the operative reports in this case furnish evidence that a complete hypophysectomy was performed. It is reasonable to assume that complete cleaning out of the sella turcica, such as was done in this case, means that the whole pituitary gland was removed. With the acceptance of this fact, therefore, we are justified in concluding that the pituitary body is not a vital organ. For a number of years it has been taught that the hypophysis is essential to life.¹ This concept, however, has not been universally accepted. Paulesco, in 1907, first succeeded in both partially and completely extirpating the pituitary in dogs and pronounced this gland a vital organ. Later Cushing, Bell and Beidl and their co-workers, using the same technic, concurred with Paulesco in the belief that the pituitary was essential to life. Van Dyke,² in a review of the recent work done on this subject, covering over 500 manuscripts, maintained that the pituitary is by no means a vital

1. Boyd, W.: *Physiology of the Pituitary Body*, in *A Textbook of Pathology*, Philadelphia, Lea & Febiger, 1932, p. 704. Towne, E. B.: *The Pituitary Body*, in *Nelson New Loose-Leaf Medicine*, New York, Thomas Nelson & Sons, 1938, vol. 3, pp. 239-256. Cushing, H.: *The Pituitary Body and Its Disorders*, Philadelphia, J. B. Lippincott Company, 1912.

2. Van Dyke, W. E.: *Physiology and Pharmacology of the Pituitary Body*, Chicago, University of Chicago Press, 1936, pp. 1-56.

organ. He claimed that most workers performing extirpation experiments have failed to take into consideration injury to the brain, which is always an accompaniment, owing to the intimate relation of the pituitary to the hypothalamus. Dandy and Reichert,³ in their experiments on dogs, likewise came to the conclusion that there was "no evidence to support and every evidence to refute the assumption that the hypophysis is essential to life." They used the transbuccal approach rather than the elevation of a bone flap and kept some of their dogs alive almost three years after complete extirpation of the gland. Baker and Craft⁴ reported the case of an 18 year old pituitary dwarf studied over a period of eight years who died after an appendectomy. Autopsy showed that only about one sixth of the normal number of anterior lobe cells remained, while changes in the posterior lobe were even more striking in that there was complete replacement by connective tissue of all normal elements. Most of the connective tissue had undergone hyalinization, so that no normal posterior lobe could be identified.

We found that the fasting blood sugar values in our case were well within the hypoglycemic range. All told, there were six reports on fasting blood sugar; the lowest value was 34 mg. per hundred cubic centimeters, and the highest was 80 mg. The average of the six values was 57 mg. It will be noted that shock was not present when these readings were made. This is in accord with the observations of Hart and Lisa⁵ that fasting blood sugar values within the hypoglycemic range without any evidence of shock are common.

Four dextrose tolerance tests were performed. Two standard curves were completed. These might be interpreted as delayed curves. A third standard curve was incomplete, but what was present could be classed as low plateau. The remaining test, which was made to show the effect of a meal, revealed little or no rise one hour after the food had been ingested. One could say from the results that the response to dextrose was somewhat erratic, with, however, a tendency toward a delayed rise in the tolerance curve and, at times, a low plateau. Because the blood sugar remains within certain levels, neither disappearing from the blood stream nor reaching diabetic values, and because the values change after the ingestion of dextrose, it is apparent that the blood sugar levels are not wholly dependent on the pituitary.

3. Dandy, W. E., and Reichert, F. L.: Experimental Hypophysectomy in Dogs, *Bull. Johns Hopkins Hosp.* **62**:122-156, 1938; Studies on Experimental Hypophysectomy: Effect on the Maintenance of Life, *ibid.* **37**:1-13, 1925.

4. Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, *Endocrinology* **26**:801-807, 1940.

5. Hart, J. F., and Lisa, J.: The Rate of Occurrence of Hypoglycemia, *Endocrinology* **27**:19-22, 1940.

Lawrence and Hewlett⁶ stated that the pituitary gland acts solely as a stabilizer of the blood sugar. This is within reason; yet there seems to be a blood sugar level-raising mechanism involved.

CONCLUSIONS

1. The total removal of the hypophysis produces a drop in the fasting blood sugar to hypoglycemic levels.
2. No shock accompanies these low values.
3. Sugar tolerance curves are somewhat erratic, with a tendency to a delayed rise and, at times, a plateau.
4. The level of the blood sugar is not wholly dependent on the pituitary gland.
5. The pituitary gland functions as a blood sugar level-raising mechanism.
6. The pituitary gland is not a vital organ.

6. Lawrence, R. D., and Hewlett, R. F. L.: Effect of Pituitrin and Insulin on Blood Sugar, *Brit. M. J.* **1**:998-1002, 1925.

BIOLOGIC FALSE POSITIVE SEROLOGIC REACTIONS IN TESTS FOR SYPHILIS

I. OCCURRENCE IN NORMAL PERSONS

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Opinion as to the specificity of serologic tests for syphilis, since their first introduction in 1906, has passed through two periods and is well on its way into a third. For the first ten to fifteen years it was generally thought that positive results might occur in relation to many diseases other than syphilis, and there is a vast literature reporting "false positive" reactions in cases of almost every known disease. In the following two decades the pendulum swung in the reverse direction. It was generally felt that, except for the results in yaws, leprosy, malaria, infectious mononucleosis and perhaps one or two other conditions, serologic tests for syphilis were amazingly specific. Technical errors excluded, when positive results were obtained either in the case of an apparently normal person or in the case of one with a clearly non-syphilitic disease, these results were regularly assumed to be due to associated asymptomatic syphilitic infection.

In more recent years doubt has again been thrown on the specificity of serologic tests for syphilis. There is now considerable evidence not only that positive results may be produced with varying frequency by a number of diseases other than syphilis but that even nonsyphilitic, clinically normal persons may occasionally yield serums that give biologic false positive reactions. These points have become especially important with the increasingly widespread use of routine serologic tests, not only as a diagnostic measure in cases of illness but as a compulsory public health measure in premarital and prenatal examinations and in the testing of industrial personnel.

The question of biologic false positive reactions in serologic tests for syphilis will therefore be considered in three papers. This, the first

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of the series, considers their occurrence in normal persons; the second ¹ discusses their incidence in patients with diseases other than syphilis; the third ² presents a tentative method of approach to the recognition of their nonspecificity.

At the outset, a clear distinction must be drawn between technical and biologic false positive results in these tests. Technical false positive results, as the term implies, are those due to one or more of many possible technical errors in the performance of the test, and are not found in repeated tests on the same serum by the same or different technics in the same or different laboratories. Included in the category of technical false positive results should probably be certain of those obtained with supersensitive flocculation technics, such as the Kline exclusion or the Kahn presumptive test, even though these results may be repeated with the same serum and the same technic in the same or different laboratories. In these supersensitive technics, specificity has deliberately been sacrificed in order to achieve maximum sensitivity, and in various serologic surveys these "screen" procedures have given up to 10 per cent or more false positive results for normal persons. It seems probable that these false flocculation reactions depend primarily on the known instability of the particular lipoidal suspensions used as antigen.

Biologic false positive reactions, by the definition of these papers, are those for which technical error can be excluded by verification in the same or in different laboratories and in which the demonstration of a positively reacting substance in the serum rests on technics other than the supersensitive flocculation tests referred to in the foregoing paragraph.

THE LITERATURE

That reagin or a reagin-like substance might be present, either intermittently or constantly, in the serums of some normal human beings was forcibly brought to the attention of clinicians by the demonstration of the fact that such a substance is present in the serums of many other normal animals. This is not a new observation, as the fact itself has been known since 1907, but the earlier papers describing it have until recently attracted little attention, either from clinicians or from serologists. Kemp, Fitzgerald and Shepherd ³ have completely reviewed the

1. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions for Syphilis: II. Tests of Patients with Organic Diseases Other Than Syphilis, *Arch. Int. Med.*, to be published.

2. Moore, J. E.; Eagle, H., and Mohr, C. F.: Biologic False Positive Serologic Tests for Syphilis: III. A Suggested Method of Approach to Their Clinical Study, *J. A. M. A.* **115**:1602 (Nov. 9) 1940.

3. Kemp, J. E.; Fitzgerald, E. M., and Shepherd, M.: The Occurrence of Positive Serologic Tests for Syphilis in Animals Other Than Man, with a Review of the Literature, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:537 (Sept.) 1940.

literature pertaining to positive reactions in serologic tests for syphilis on animals other than man and have presented original observations on specimens from chickens, pigeons, rabbits, mice, cattle, sheep, horses and swine. They concluded:

Personal experience and a review of the literature show that a large number of animals other than man have been found to have positive serologic tests for syphilis. Our findings, using a variety of tests for the examination of the sera of numerous animals, are in agreement with those of other observers. Our findings also confirm earlier observations that there is marked discrepancy between the results of the different tests in different animal species and the results of identical tests in the same animal species. Quantitative determination of the amount of reacting substance in the blood of animals shows that, as determined by the Eagle microflocculation test, it is less in amount than in the serum of known syphilitics. In two animal species, dogs and cattle, and probably sheep as well, the number of positive tests increased with increasing age of the animals.

The possibility that the serum of man, like that of other animals, might contain reagin or some reagin-like substance in the absence of syphilitic infection has of course not escaped the attention of serologists, though little stress has been laid on it. Browning,⁴ Meinicke⁵ and Hinkleman⁶ have all contended that the difference between normal and syphilitic human serum is merely one of degree, and not of kind, and in that connection have stressed the nonspecific nature of the lipoidal "antigen" and of the "reagin" with which it combines. The more recent demonstration by Eagle⁷ that the physical mechanism of the Wassermann and flocculation tests for syphilis is precisely that of specific antigen-antibody reactions, and the further demonstration by Beck⁸ and by Eagle and Hogan⁹ that syphilis reagin itself is probably an antibody to *Spirochaeta pallida* which happens to cross react with tissue lipoids, may help clarify the *raison d'être* of these tests but does not exclude the possibility that a substance reacting in a manner similar to this antibody may occasionally be present in the serum of normal

4. Browning, C. H.: Biochemistry of Immune Reactions, Brit. M. J. **1**:239, 1915.

5. Meinicke, E.: Zur Theorie und Methodik der serologischen Luesdiagnostik, Deutsche med. Wchnschr. **45**:178 (Feb. 13) 1919.

6. Hinkleman, A. J.: Biochemistry of the Wassermann Reaction, Am. J. Syph., Gonorr. & Ven. Dis. **11**:594 (Oct.) 1927.

7. Eagle, H.: Studies in the Serology of Syphilis: I. Mechanism of the Flocculation Reactions, J. Exper. Med. **52**:717 (Nov.) 1930; II. The Physical Basis of the Wassermann Reaction, *ibid.* **52**:739 (Nov.) 1930.

8. Beck, A.: The Role of the Spirochaete in the Wassermann Reaction, J. Hyg. **39**:298 (May) 1939.

9. Eagle, H., and Hogan, R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes: Their Relation to So-Called Wassermann Reagin and Their Significance for the Serodiagnosis of Syphilis, J. Exper. Med. **71**:215 (Feb.) 1940.

human beings in concentration sufficient to give a positive result in a Wassermann, flocculation or even spirochetal complement fixation test.

The experimental evidence that normal human serum may contain reagin or a reagin-like substance is summarized in the following paragraphs.

In 1931 Malloy and Kahn¹⁰ observed that when normal serum was mixed with standard Kahn antigen, microscopic aggregates formed slowly. No aggregates were visible when the mixture was examined immediately; after the mixture had stood one hour, the average size of the aggregates was 60 square microns, and after it had stood six hours, 190 square microns. In contrast, the average size of the aggregates formed by mixing syphilitic serum with standard Kahn antigen was 420 square microns when the mixture was examined immediately, 1,730 square microns after the mixture had stood one hour and 4,260 square microns after it had stood six hours. When normal serum was mixed with a sensitized antigen (that used in the Kahn presumptive test) and the mixture examined immediately, the aggregates measured on the average 40 square microns; after one hour they measured 470 square microns, and after six hours, 1,010 square microns. Corresponding figures for a mixture of syphilitic serum and sensitized antigen were 425, 1,020 and 3,160 square microns. The authors concluded:

It is evident from these experiments that nonsyphilitic serums also show aggregates after contact with antigenic suspension. It appears that the difference between nonsyphilitic and syphilitic serums is one of degree rather than of kind—quantitative rather than qualitative. In syphilis, there seems to be a marked increase in the property possessed by nonsyphilitic serum to aggregate the lipid particles of the antigenic suspension. When the results obtained with the two antigens are compared, the averages of the extent of aggregation are higher with standard antigen than with sensitized antigen in the case of syphilitic serums, while the reverse is true in the case of nonsyphilitic serums.

In 1934 Schreus and Foerster¹¹ described a method for the demonstration of small quantities of reagin in the serums of syphilitic patients whose Wassermann reactions were negative. When subliminal amounts of a serum of known positive titer, less than would be necessary to give a positive Wassermann reaction, were added to the apparently negative serums, the latter gave positive results, presumably because of an additive effect. The following year Barnett, Jones and Kulchar,¹² using the Kline

10. Malloy, A. M., and Kahn, R. L.: The Ultramicroscopic Precipitation Reaction in Syphilis, *J. Infect. Dis.* **48**:243 (March) 1931.

11. Schreus, H., and Foerster, R.: Spezifische Sensibilisierung von serologischen Reaktionen: Grundlage und Methodik der spezifisch sensibilisierten Wassermann-Reaktion (WSR.), *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **82**: 53, 1934.

12. Barnett, C. W.; Jones, R. B., and Kulchar, G. V.: Measurement of Reagin in Nonsyphilitic Sera, *Proc. Soc. Exper. Biol. & Med.* **33**:214 (Nov.) 1935.

test, adapted this technic to the demonstration of reagin in normal serums. They concluded:

Reagin is evidently present in the sera of non-syphilitic individuals. There is no proof that this reagin is identical with that found in syphilitic sera but it reacts in the same way to the Kline precipitation test. The difference between syphilitic and non-syphilitic sera seems to be a quantitative rather than a qualitative one.

We have repeated the experiments of Barnett and his collaborators, and are able to confirm their observation that normal serum contains a substance that will react with the antigen used in the Kline test. Although our own experiments, to be reported in a following paper, indicate that this normal reagin differs qualitatively from that of syphilitic serum, it nevertheless seems clear that the reactive factor of normal serum is a potential source of error, certainly for the Kline test, and perhaps for other flocculation tests as well.

Sherwood and his associates¹³ have developed a technic which they designate as the "widespread Kahn test." A series of tubes is set up in which the serum: antigen ratio varies from 1:100 to 1:5, as compared with the ratios of 1:12 to 1:3 used in the standard diagnostic test. Serums from normal persons are sometimes found to be positive with the higher serum: antigen ratios (1:100 to 1:40), though negative with lower ratios as used in the diagnostic Kahn test and negative with all other standard diagnostic tests. Sherwood and his co-workers found this phenomenon in 12 of 1,018 serums from healthy white college students. The implication that these serums contain a reactive factor resembling that of syphilitic serum requires no discussion.

More recently Eagle¹⁴ has approached the problem afresh from a clinical-statistical point of view. In order to estimate the probable incidence of biologic false positive reactions in the tests of normal persons, he selected a large population in whom the incidence of syphilis might properly be assumed to be very small because of age, social and educational status and other factors, i. e., white university students, both male and female. The serums of 40,545 students from twenty-five universities in various parts of the United States were examined. When positive results were obtained, the patients were carefully examined by physicians of the various student health services. An earnest effort was made, by means of careful history taking, physical examination and, often, examination of other members of the family, to determine whether

13. Sherwood, N. P.; Bond, G. C., and Canuteson, R. I.: On the Possible Presence of a Reagin-Like Factor in Normal Human Serum, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:179 (March) 1941.

14. Eagle, H.: On the Specificity of Serologic Tests for Syphilis as Determined by 40,545 Tests in a College Student Population, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:7 (Jan.) 1941.

the positive results obtained were due to (1) technical error, (2) syphilitic infection or (3) the factor in normal serum which gives biologic false positive results in such tests. Among the 40,545 students, the initial tests showed positive results for 73, doubtful for 117. Thirty-three of the positive and 95 of the doubtful results could be dismissed as due to technical error, since the reactions to succeeding tests were always negative and these students showed no evidence of syphilis. Twenty-six of the students with positive and doubtful results were shown to have syphilis. There remained, however, 36 students with repeatedly positive or doubtful results for whom there was neither history nor physical or collateral evidence of syphilitic infection and whose reactions might be regarded as of the biologic false positive type. This is an incidence of 1 false positive reactor in every 1,125 students tested. However, those universities with the highest incidence of syphilis also had the highest incidence of apparent biologic false positive results. Correcting statistically for this fact, Eagle estimated that with present day serologic tests the incidence of biologic false positive results in tests on the population studied is of the general magnitude of 1 for every 4,000 persons tested, and perhaps even less.

Eagle quite properly suggested that from the standpoint of public health the low incidence of biologic false positive results observed in his series creates no problem and that it is perhaps justifiable from this point of view to regard all persons with positive serum reactions as syphilitic and to treat them as such. He agrees, however, that from the point of view of the individual patient such an attitude is sometimes not justifiable. The diagnosis of syphilis has many serious implications, social, mental and physical, and antisyphilitic treatment is not without danger to health, or even life, to say nothing of its inconvenience and expense. The discovery of a positive serologic reaction for syphilis in a case in which there is no history of infection or physical evidence of this disease is therefore one which calls for the utmost care in determining the validity of the result.

That apparently normal persons may temporarily or permanently possess reagin or a reagin-like substance in their bloods which reacts positively in standard serodiagnostic tests for syphilis is shown by the following case reports. The persons concerned have all been observed in the private practice of one of us (J. E. M.). They have been studied by the methods outlined in the third paper of this series,² though it must be emphasized that all of the procedures there advised have not been employed in any one case, since to include them all was usually neither necessary nor feasible.

REPORT OF CASES

CASE 1.—A white man aged 28, an attorney, was required by his employer to have a yearly physical examination. In the course of the examination, on Jan.

7, 1936, he was found to have a positive reaction for syphilis. There was no history of syphilitic or gonococcal infection. On detailed physical examination there was no evidence of acquired or congenital syphilis. At no time had the patient received antisyphilitic treatment. There was no evidence of any other infectious disease. The only abnormal physical findings were small varicose veins of the right leg, leukoderma of the penis, present since childhood, and flat feet. With the exception of the serologic reaction for syphilis, the results of routine laboratory studies were negative. Particularly was there no evidence of infectious mononucleosis or malaria. The patient's mother denied having had syphilitic infection, and her reactions to serologic tests were entirely negative. The serologic tests are summarized in table 1. This patient's blood was tested in five different laboratories, and according to four of them a small quantity of reagin was present over a seven week period. Eleven weeks and again three years after the first visits the reactions were negative, and the patient remains well. No treatment was given.

TABLE 1.—*Serologic Tests for Syphilis, Case 1**

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation	Eagle Micro-flocculation	Kline Diagnostic	Hinton
1/ 7/36	1	0	P
2/ 2/36	2	0	D	D
	3	D	D
2/ 3/36	2	0	D	D
	3	0	0
2/23/36	4	0	0
	5	P (3 units)	..
2/24/36	5	P	..
4/23/36	2	0	0	0
4/ 3/39	2	0	0	0

* In this table and in subsequent tables, laboratories are designated as 1, 2, 3, etc. Results of serologic tests are expressed as positive (P), doubtful (D), negative (0) and anticomplementary (A.C.). If a quantitative titration in a positive test was performed the titer, expressed in units of reagin (serum dilution), is parenthetically inserted after the positive result.

CASE 2.—A white man aged 25, a clerk, presented himself to his local physician in January 1937 for a premarital examination. At the time of this examination he was found to have a positive Wassermann reaction. The patient was seen by one of us (J. E. M.) on March 13. He denied having had gonorrhea or any lesions suggestive of syphilis. He admitted only one sexual exposure, five years before the present examination. After this exposure he had had six serologic tests for syphilis over a period of five years, all of which gave negative results. The patient had no subjective or objective signs or symptoms of syphilis at the time of examination, nor had he any signs or symptoms of any other organic disease. About five weeks prior to the examination the patient had been circumcised, and there was still slight induration in the circumcision scar. In 1934 he had malaria, which was adequately treated, and apparently there had been no recurrences. The results of the routine laboratory studies, with the exception of those in the serologic tests for syphilis, were entirely negative. A careful search was made for malarial parasites, but none could be found. (Even if a patient were a chronic carrier of undemonstrable malarial parasites, there is no information available in the literature

or in our own experience to indicate that this symptomless carrier state can produce false positive serologic results in tests for syphilis. Indeed the available evidence indicates that false positive serologic reactions in cases of malaria occur only during or shortly after the acute febrile illness.) A test for heterophil antibody gave a negative result. Complement fixation tests with gonococcus, staphylococcus and streptococcus filtrates were all positive. Especial emphasis is directed toward this nonspecific tendency to positive complement fixation with widely varying antigens. The serologic tests for syphilis are summarized in table 2.

A "provocative" injection of neoarsphenamine, 0.6 Gm., was given on March 13, 1937, but no other antisyphilitic treatment. During the first three months of 1937 this patient's blood was tested in five different laboratories by three different technics. Reagin was constantly present in small quantities during this period,

TABLE 2.—*Serologic Tests for Syphilis, Case 2*

Date January 1937 (several tests done elsewhere)	Laboratory	Wassermann P on 3 occa- sions in 2 different laboratories	Kahn Standard P once, D 4 times in 3 different laboratories	Eagle Macro- flocculation	Eagle Micro- flocculation
3/13/37	1	P	0	D	..
	2	D	D
	3	D	D
3/15/37	1	P (2.5 units)	..	D	..
3/17/37	1	0	D	D	..
	2	0	0
3/18/37	1	0	D	D	..
	2	0	0
3/19/37	1	P (2.0 units)	D	D	..
	2	P (12.0 units)	P
3/20/37	1	P (2.5 units)	D	D	..
	2	P (18.0 units)	P
3/21/37	1	P (2.5 units)	P
	2	P (18.0 units)
3/24/37	1	0	0	0	..
	2	D	D
2/22/38	1	0	0	0	..
5/15/39	1	0	0

and there was an apparent "provocative" rise in the reported titers from one laboratory following the injection of neoarsphenamine. Eventually the reagin disappeared, and two years later the patient was well and his serum still gave a negative reaction.

CASE 3.—A white man aged 38, a physician, volunteered, about Nov. 1937, to give blood for experimental work which was being done on a new flocculation test. The serum was found to give a positive reaction with this test, and therefore the result was checked with standard tests. In the standard tests the serum gave either positive or doubtful results. The patient denied having had premarital or extramarital exposure and gave no history of primary or secondary syphilitic lesions. He had had several serologic tests for syphilis performed while he was in college and medical school, all of which gave negative reactions. He did state, however, that in May 1937, while cleaning a syringe and needle after venipuncture, he stuck the needle under his finger nail. There resulted a sore which did not heal for two weeks. This lesion contained pus and was painful. The patient did not know the

serologic status of the person on whom he did the venipuncture. There were no subsequent lesions which might have been significant. At the time of examination, Nov. 6, 1937, there were no subjective or objective signs or symptoms of syphilis, nor were there any signs or symptoms of any other organic disease. The routine laboratory studies gave negative results. A lumbar puncture was performed, and the cerebrospinal fluid was entirely normal. A test for heterophil antibody gave a negative reaction. Examination of the patient's wife, with whom he had had unrestricted sexual intercourse during the time when, if he had had early syphilis, the disease might have been expected to be most infectious, gave wholly negative results. The serologic tests are summarized in table 3. Small quantities of reagin were constantly demonstrable in six different laboratories by seven different technics over a period of six months. Since in the recent past repeated serologic tests had given negative results, the positive results appearing in the fall of 1937,

TABLE 3.—*Serologic Tests for Syphilis, Case 3*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation	Eagle Micro-flocculation	Hinton	Kline Diagnostic	Laughlen
11/ 6/37	1	D	D	P
	2	D	P	D
	3	0	D
11/18/37	1	P (8 units)
	2	0	D	D
11/24/37	2	0	D	0
12/ 1/37	1	P	P
12/ 8/37	1	0	0
	2	P (2 units)	P	P
12/14/37	2	P (1 unit)	P	P
12/16/37	2	P (1 unit)	P	P
12/17/37	2	P (1 unit)	P	P
12/18/37	2	P (1 unit)	P	P
12/20/37	2	P (1 unit)	P	P
2/ 2/38	4	D	..
	5	P	D	D	..
	6	P
2/20/38	2	P (1.5 units)	P	D
4/20/38	2	P (1.5 units)	D	P

if due to syphilis, should have represented an early stage. One might, therefore, expect the serum titers to be consistently high, instead of, as actually observed, constantly low over a six month period without treatment.

CASE 4.—A white woman aged 25, single, consulted a physician in June 1931 because of abdominal pain. At the age of 10 she had had several sexual exposures with a 14 year old boy. The patient had not had intercourse since that time. She had no subjective or objective signs or symptoms of acquired or congenital syphilis, nor had she any signs or symptoms of any other organic disease. No organic basis could be found for the abdominal pain except that the patient was somewhat nervous and undernourished. The patient's mother denied having had syphilitic infection, and Wassermann, Kahn and Eagle tests performed on the mother's serum gave negative results. All routine laboratory studies made on the patient gave negative results with the exception of the serologic reactions for syphilis. The Wassermann tests were unusual inasmuch as those made with dilutions between 1:5 and 1:80 gave

on most occasions positive or doubtful results, whereas all those made with dilutions lower and higher than these were negative. Complement fixation tests were performed with a cholesterolized extract of sheep cells and a cholesterolized extract of milk. With both of these nonspecific antigens the serum reacted positively, and the same zone phenomenon was seen as with specific antigens. The serologic tests for syphilis are summarized in table 4. The discrepancy between the reactions to the several serologic tests for syphilis, the positive results obtained with wholly nonspecific

TABLE 4.—*Serologic Tests for Syphilis, Case 4*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation
6/11/31	1	P	P	0
6/12/31	1	P (1:2 to 1:100)	0	0
	2	P (1:5 to 1:64)	0	0
6/17/31	1	P (22 units)	0	0
6/20/31	1	P	0	0
	2	P	0	0
	3	0
	4	D in dilution 1:5
6/21/31	Neoarsphenamine 0.6 Gm. as provocative			
6/22/31	1	P
6/23/31	1	D in dilutions 1:5 to 1:30
6/25/31	1	D in dilutions 1:10 to 1:20	0	0
6/27/31	2	D in dilutions 1:10 to 1:80	0	0
6/29/31	1	D in dilutions 1:10 to 1:20	0	..

TABLE 5.—*Serologic Tests for Syphilis, Case 5*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation	Eagle Micro-flocculation	Kline Diagnostic	Hinton	Kline Exclusion	Kahn Presumptive
10/14/38	1	..	P
10/20/38	1	..	P
10/24/38	2	P (66 units)	0	0
10/25/38	2	P (25 units)	0	0
	3	P (24 units)	0	..	0	0	0
	4	P (18 units)	0
10/28/38	2	P (25 units)	0	0
	5	0	0
11/ 1/38	6	D	D	0
	7	..	D	P
	8	0	..	0	..
11/ 8/38	5	0	0
3/30/39	2	0	0	0

antigens, the absence of a history of syphilis and indeed the probable lack of opportunity for acquiring it, the freedom from physical evidence of syphilis or of any other disease, all justify the classification of this patient as nonsyphilitic.

CASE 5.—A white man aged 25, an accountant, was found, on Oct. 14, 1938, because his employer demands yearly physical examinations, to have a positive serologic reaction for syphilis. He gave no history of syphilitic infection and had had only three sexual exposures—in June 1936, January 1938 and May 1938. Serologic tests for syphilis were negative in January 1938. There was nothing

in the history to suggest either acquired or congenital syphilis. He did have a head cold two days after the first positive serologic reaction, but this cold had disappeared before he was examined by us. The patient had no objective or subjective signs or symptoms of syphilis. There was no evidence of any other organic disease. All routine laboratory studies gave negative results. The reaction to a test for heterophil antibody was negative. A complement fixation test done with spirochetal antigen¹⁵ gave a negative result. The serologic picture resembled that often observed in infectious mononucleosis inasmuch as the complement fixation test gave a strongly positive reaction (66 units) at a time when the results of flocculation tests were negative or doubtful, but there was no clinical or other laboratory evidence justifying such a diagnosis. A definite zone phenomenon was noted in the quantitative Wassermann test. The serologic tests for syphilis are summarized in table 5. The spontaneous reversal of the serologic result and the absence of any other evidence for syphilis or any other infectious disease justify the diagnosis of false positive reactions occurring in tests of a normal person.

CASE 6.—A white man aged 26, an officer on a steamship, had had occasional attacks of pain in the lower right quadrant of the abdomen in the past two years.

TABLE 6.—*Serologic Tests for Syphilis, Case 6*

Date	Laboratory	Wassermann	Eagle	Kahn	Kline Diagnostic	Hinton	Kline Exclusion	Sigma
1/31/39	1	0	P	0	0	..	D	..
2/ 2/39	1	0	P	0	0	..	D	..
2/ 7/39	1	0	D	..	0	..	D	..
2/ 8/39	2	0	0	0	0	P
7/15/39	3	0	..	0	0

Because he was at sea for long periods, he was advised by the physician of the steamship company to have his appendix removed, even though he was symptomless at the time. An appendectomy was performed on Jan. 31, 1939, and a chronically inflamed appendix was removed. Before the operation routine serologic tests for syphilis were done and the results reported as doubtful. The patient had no subjective or objective signs or symptoms of syphilis or of any other disease. He had had only one sexual exposure in his life, two years previously. His mother and father are living and well; there is no history of lesions suggestive of congenital syphilis in his brothers or sisters. Routine laboratory studies gave negative results. The serologic tests for syphilis are summarized in table 6.

CASE 7.—A white man, aged 32, a musician, consulted his physician on Feb. 2, 1940, because of "fluttering of his heart." The symptoms had been present only a few days. There was no history of precordial pain, dyspnea, cough or edema of the ankles. Two or three weeks before examination he complained of substernal oppression, which has since disappeared.

He gave no history of either acquired or congenital syphilis. The results of his mother's serologic tests for syphilis were negative. The patient stated that at one time he had a small abscess on the shaft of the penis, which was opened and

15. The antigen used was palligen, commercially available in Germany. Although the exact method of preparing the antigen has not been published, it is based on phenolizing cultures of the Reiter strain of *S. pallida*.

drained and which disappeared in two days. During the period of observation concerned here he had another such abscess in a hair follicle at the base of the penis. He had had slight albuminuria for thirteen years. His physical examination showed nothing abnormal. Routine laboratory examination gave normal results except for slight albuminuria. There was no disturbance of renal function. The cerebrospinal fluid was normal. The serologic tests for syphilis are summarized in table 7.

TABLE 7.—*Serologic Tests for Syphilis, Case 7*

Date	Laboratory	Wassermann	Eagle	Kahn Diagnostic	Kline Diagnostic	Hinton	Kahn Presumptive	Kline Exclusion
2/ 7/40	1	0	D
2/12/40	1	0	D
	2	D	..	0
2/26/40	1	D	D
	2	P	..	D
3/11/40	1	0	D
	2	P	..	0
3/25/40	3	0	..	0
4/10/40	4	P	P
	5	0	0	0
4/30/40	6	..	0	..	D	D
	7	0	0	0	0
	8	0	D	..

TABLE 8.—*Serologic Tests for Syphilis, Case 8*

Date	Laboratory	Complement Fixation	Eagle Macro-flocculation	Eagle Micro-flocculation	Kahn Diagnostic	Kahn Presumptive	Kahn Verification	Kline Diagnostic	Kline Exclusion	Palligen
4/22/38	1	0	D	D	..
4/28/38	1	0	D	D	..
	2	A C.	D	..	D
9/19/38	1	0	D	D	..
4/19/40	3	0
	1	0	D	P	..
4/30/40	4	D	D	..
	5	D	D	..
	1	0	D	D	..
5/ 2/40	2	0	0	..	0
5/ 9/40	3	0	..	0	D	P
	1	0	D	P	..
	4	D	D	..
	5	D	D	..
	6	0
	7	D	P	0
	2	0	0	..	0

CASE 8.—A white woman aged 55, a seamstress, consulted a physician two years ago (April 1938) because of swelling of the left middle finger and pain in the knee joints. At the time of this consultation serologic tests for syphilis were done and the results reported as doubtful. Within three months of this discovery the arthralgia spontaneously disappeared. Serologic tests were done on two occasions in 1938, with essentially similar results. In April 1940 she consulted her physician again for routine examination. He repeated the serologic tests and, confronted with

identical results, referred her to us. At this time (1940), she has no complaints, and gives no history of either acquired or congenital syphilis. A physical examination has shown her to be in excellent health. The cerebrospinal fluid is normal.

The patient is married; her husband is well and his serologic reactions for syphilis are negative. She has two children living and well; serologic tests for syphilis were done in the case of one child and the results were negative.

Routine laboratory studies yielded negative information. The serologic tests for syphilis of this patient are summarized in table 8. No antisyphilitic treatment has been given at any time.

CASE 9.—A white man aged 26, an officer in the United States Navy, with no personal or familial history suggesting syphilis, applied for a marriage license in

TABLE 9.—*Serologic Tests for Syphilis, Case 9*

Date	Lab- ora- tory	Wasser- mann	Kahn Diag- nostic	Kahn Pre- sump- tive	Kahn Veri- fication	Kline Diag- nostic	Kline Exclu- sion	Eagle Floccu- lation	Hinton	Palli- gen
8/19/39	1	0	..	0
8/—/39	2	..	D
9/—/39	2	..	P	P
	3	..	P	P
10/26/39	1	P	..	P
	4	0	D	D
	5	0	P	D	D
11/—/39	6	0	D	..	P	..	0
11/27/39	1	P	..	P
	4	0	D	D
	5	0	D
	7	0
1/30/40	3	..	P	P
2/19/40	3	Cerebrospinal fluid completely normal								
4/ 1/40	3	..	D	P
	5	0	P	D	D	P
	8	0	D
6/ 5/40	9	0	P	D
	2	..	0	D	0
	10	0	0	D	..
	11	D	D	D
	6	0
6/16/40	9	0	D	D
	12	0	0	0	0	0
	6	0

Michigan in August 1939. The serologic tests required by law were performed in another state (laboratory A) and the results were reported negative. Since this laboratory was not approved by the Michigan State Department of Health, other tests were required from a Michigan laboratory (B); those done about one week after the first tests gave doubtful results, and those done one week later still (in two laboratories, B and C) gave positive reactions. These results caused the refusal of a marriage license and initiated a long and extensive investigation for syphilis, which has now lasted for ten months and has caused two hospital admissions, two separate examinations of the cerebrospinal fluid (both showing the fluid to be normal) and laboratory studies in twelve different laboratories by nine different technics on eleven different samples of blood. These tests are summarized in table 9.

From the anamnestic standpoint, not only is a history of syphilis lacking, but there has been only one sexual exposure, with a social equal, in the summer of 1936. The original positive serologic reactions in August 1939 were not preceded

by any recognizable acute infection. His physical status, as determined by several observers over the ten month period of investigation, has always been normal, and there are no abnormalities suggesting syphilis.

The serologic picture is somewhat beclouded by the facts that (1) on Oct. 27 and Nov. 1, 1939 two injections each of neoarsphenamine (0.35 and 0.4 Gm) and of bismuth subsalicylate (each 0.2 Gm.) were given (but there was no effect from this on subsequent serologic tests) and (2) no quantitative titrations were performed. By the time the patient reached our hands, in June 1940, the quantity of reacting substance in his blood was too small for quantitation.

All other laboratory studies in June 1940, including examination of blood smears for malaria and infectious mononucleosis, examination of serum for heterophil antibody and determination of the sedimentation rate, gave negative results.

From the purely serologic standpoint it is to be noted that (1) the quantity of reacting substance in the blood has always been small (many doubtful results interspersed with the positive), (2) the supersensitive Kline exclusion test has always given a doubtful result when less sensitive tests showed positive results, (3) the complement fixation test with spirochetal antigen has given negative results on three occasions over an eight month period and (4) the Kahn "verification test" has given a negative result.

The conclusion is inescapable that this patient is a normal nonsyphilitic person with biologic false positive serologic reactions.¹⁶

COMMENT

We have reported 9 examples of what we regard as biologic false positive reactions to serologic tests in normal, nonsyphilitic persons. It is only fair to say that various readers may not agree with our interpretation. Indeed, before our own doubts arose as to the almost absolute specificity of serologic tests, we ourselves would have regarded some or all of these patients as having latent syphilis.

The demonstration by three different groups of workers (Malloy and Kahn; Barnett, Jones and Kulchar; Sherwood, Bond and Canute-son) that some normal human serums may contain reagin or reagin-like factors is of obvious significance for the practical serologic diagnosis of syphilis. It is true that the amount of reactive material which these workers have been able to demonstrate is well below the threshold concentration which can be detected by the standard diagnostic procedures. Under ordinary circumstances the reactivity of normal serum therefore does not complicate the diagnostic test. The 9 cases here presented, nevertheless, indicate that in the exceptional case this normal factor may be present in sufficient concentration to give biologic false reactions.

Despite these false reactions, it may be that the antibody present in syphilitic serum is strictly specific and that normal serum contains other substances with qualitatively similar effects on the lipoidal suspensions used as "antigen." Thus, a normal serum may be capable of causing the aggregation of these lipoidal suspensions to give clumps indistinguishable

16. Further tests on this patient have continued to show wholly negative results as late as Oct. 1, 1941.

from those caused by syphilitic serum, despite the fact that the mechanism of the aggregation may be altogether dissimilar. We shall discuss in a later paper ways and means which are now available to differentiate nonspecific reactions from those actually due to syphilitic infection.

CONCLUSIONS

We have reviewed the literature on the presence of a reagin-like substance in normal serum and have briefly described 9 cases in which we believe the serums of normal persons gave biologic false positive reactions for syphilis.

PROGNOSTIC VALUE OF VARIOUS CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF ACUTE MYOCARDIAL INFARCTION

I. IMMEDIATE PROGNOSIS

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Within the past thirty years myocardial infarction has risen from the position of a purely pathologic entity to the ranks of those diseases which are of first importance to the clinician. Those observers who were responsible for this rise include Dock,¹ Obrastzow and Straschesko,² Hochhaus³ and Herrick,⁴ all of whom were instrumental in first calling attention to the clinical picture of the disease. They were soon followed by a large group of others⁵ who made many valuable contributions. Beginning with the work of Smith⁶ and Pardee,⁷ a great number of electrocardiographic studies⁸ not only provided a means of

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1. Dock, G.: Notes on the Coronary Arteries, Ann Arbor, Mich., The Inland Press, 1896.

2. Obrastzow, W. P., and Straschesko, N. D.: Zur Kenntnis der Thrombose der Koronararterien des Herzens, Ztschr. f. klin. Med. **71**:116, 1910.

3. Hochhaus, H.: Zur Diagnose des plötzlichen Verschlusses der Kranzarterien des Herzens, Deutsche med. Wchnschr. **37**:2065, 1911.

4. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912.

5. (a) Levine, S. A., and Tranter, C. L.: Infarction of the Heart Simulating Acute Surgical Abdominal Conditions, Am. J. M. Sc. **155**:57 (Jan.) 1918. (b) Wearn, J. T.: Thrombosis of the Coronary Arteries with Infarction of the Heart, *ibid.* **165**:250 (Feb.) 1923. (c) Gardinier, H. C.: Coronary Arterial Occlusion: A Perfectly Definite Symptom Complex, *ibid.* **168**:181 (Aug.) 1924. (d) Hamman, L.: The Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**:273 (April) 1926.

6. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

7. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, with Special Reference to the Coronary T Wave, Am. J. M. Sc. **169**:270 (Feb.) 1925.

8. (a) Robinson, G. C., and Herrmann, G.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart **8**:59 (Feb.) 1921.

(Footnote continued on next page)

confirming the diagnosis but made it possible to localize the area of necrosis in the heart muscle with a high degree of accuracy. As a result of these advances myocardial infarction has become "an easily diagnosable disease" (Christian⁹). In spite of this progress in knowledge of the condition, prognosis in cases of myocardial infarction remains uncertain. As Levine¹⁰ has put it, "there are few diseases in which the prognosis in any individual case is more difficult to predict than in coronary thrombosis." Levy¹¹ concurred in this opinion, while Glendy, Levine and White¹² have indicated that it holds true as well for coronary disease in early life.

The general immediate mortality of an attack of myocardial infarction at first was thought to be about 50 per cent. In later publications this figure was reduced to 24 per cent,¹³ and even 8 per cent.¹⁴ This decrease in the immediate mortality was due not so much to any improvement in the manner of treatment but rather to a greater accuracy in diagnosis. As a result, many cases of mild infarction were discerned that formerly would not have been recognized or would have been regarded as questionable. So far, the physician has had little to guide him in predicting the immediate outcome in any specific case. It is our purpose here to review in detail the cases of a large number of patients suffering from their first attack of myocardial infarction in order to determine whether there are any clinical or electrocardiographic features which will lead to more accurate prognosis in individual cases.

(b) Willius, F. A., and Barnes, A. R.: Myocardial Infarction: An Electrocardiographic Study, *J. Lab. & Clin. Med.* **10**:427 (March) 1925. (c) Rothschild, M. A.; Mann, H., and Oppenheim, B. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Artery Occlusion, *Proc. Soc. Exper. Biol. & Med.* **23**:253 (Jan.) 1926. (d) Wilson, F. N.; Macleod, A. G.; Barker, P. S.; Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* **16**:155 (June) 1933. (e) Barnes, A. R.: *Electrocardiographic Patterns: Their Diagnostic and Clinical Significance*, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

9. Christian, H. A.: Coronary Thrombosis: An Easily Diagnosable Disease, *Am. Heart J.* **1**:129 (Dec.) 1925.

10. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Baltimore, Williams & Wilkins Company, 1929.

11. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936, chap. 8.

12. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth: A Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, *J. A. M. A.* **109**:1775 (Nov. 27) 1937.

13. Howard, T.: Coronary Occlusion, Based on the Study of One Hundred and Sixty-Five Cases, *M. Times & Long Island M. J.* **62**:337 (Nov.) 1934.

14. Master, A. M.; Jaffe, H. L., and Dack, S.: The Treatment and Immediate Prognosis of Coronary Artery Thrombosis, *Am. Heart J.* **12**:549 (Nov.) 1936.

MATERIAL AND METHOD

In this portion of the study (part I) a review was made of the cases of all patients entering the Peter Bent Brigham Hospital between December 1935 and June 1940 whose diagnosis at discharge included myocardial infarction. From these patients were selected, in consecutive fashion, all those whom we believed to be suffering from their first attack. We have thus avoided the confusion in both the clinical and the electrocardiographic picture which so often arises when one is dealing with patients who have suffered multiple attacks. Only those patients were included for whom the diagnosis was felt to be definite. A large percentage of the patients were seen by one or both of us. Each case record was analyzed in detail, and the electrocardiograms were reviewed. On the basis of the electrocardiograms the entire series of patients was divided into six groups distinguished by the presence of (1) anterior infarction, (2) posterior infarction, (3) bundle branch block, (4) partial or complete block, (5) defective intraventricular conduction or (6) low voltage of the QRS complex in the standard three leads. A seventh, unclassified group included patients for whom the changes were not distinctive but the diagnosis was certain from clinical evidence alone. In addition, 1 patient with infarction of the right anterior ventricular wall was included in the series. That we were dealing with patients in whom infarction was recent was indicated by the fact that 82 per cent of them had electrocardiograms within the first five days of the time of onset of symptoms. Under the term immediate mortality we included death within one month after the onset of the attack, either from the infarction or from its complications.

In analyzing the prognostic significance of the various clinical features, such as pain, dyspnea, cyanosis and shock, we appraised their presence and development throughout the early hours and days of the disease. It obviously would be futile to regard in the same light a patient who showed shock or dyspnea only an hour or so before he died after having been free from these symptoms for a week and one who manifested similar features at the onset of the attack. In this way an attempt was made to find out the prognostic value of various aspects of the clinical symptoms of coronary thrombosis as they present themselves in general practice.

NUMBER OF PATIENTS AND MORTALITY

In the four and one-half year period covered by this study there were 208 patients whose cases fitted the limitations set forth in the preceding sections. Those patients who died as a result of this first attack or its complications totaled 68, or 33 per cent. This is a figure which we recognize as being definitely higher than the 8 per cent of Master, Jaffe and Dack,¹⁴ the 16.2 per cent found by Conner and Holt¹⁵ or the 24 per cent cited by Howard.¹³ However, all our patients were sick enough to require admission to a hospital, and thus the series does not include those with a milder form of illness who did not come to a physician until after they had recovered or who could be cared for at home. Moreover, the mortality in this series is definitely lower than in those reported by Levine (53 per cent),¹⁰ Clark (48 per cent)¹⁶

15. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, *Am. Heart J.* 5:705 (Aug.) 1930.

16. Clark, L. J.: Prognosis in Coronary Disease, *New Orleans M. & S. J.* 86:365 (Dec.) 1933.

and Cooksey (39.6 per cent),¹⁷ in which patients suffering initial and recurrent attacks were not separated. This is in agreement with the general feeling of most observers¹⁸ that the possibility of a fatal outcome increases with each attack.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Dividing the entire series into groups depending on the electrocardiographic changes yielded the following information (table 1): Anterior infarction was present in 109 patients, or slightly over one half of the total; patients with a lesion in this location had a mortality of 30 per cent. Those with posterior infarction totaled 64, with a mortality of 36 per cent, slightly higher than that in the former group. For some time there has been disagreement in the literature regarding this point, and it was this very question which initiated the present study.

TABLE 1.—*Distribution of Two Hundred and Eight Patients with Initial Acute Myocardial Infarction According to Electrocardiograms*

Group	Number of Patients	Number of Deaths	Mortality, Percentage
Anterior infarction	109	33	30.0
Posterior infarction	64	23	36.0
Bundle branch block	9	7	78.0
Partial and/or complete heart block.....	7	3	43.0
Low voltage of QRS complex in standard leads..	3	0	0.0
Defective intraventricular conduction	3	0	0.0
Unclassified	12	1	8.0
Right ventricular infarction *.....	1	1	100.0
Total.....	208	68	32.7

* Localization in the case of this patient was made at a postmortem examination.

Vander Veer and Brown,¹⁹ Stroud²⁰ and Wood and associates²¹ have expressed the belief that anterior myocardial infarction is far more serious than one involving the posterior wall of the left ventricle. Our results tend to confirm the conclusion of Master and co-workers¹⁴ and of Willius¹⁸ that the mortality in the two groups is practically identical.

17. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Especial Reference to Prognosis, *J. A. M. A.* **104**:2063 (June 8) 1935.

18. Willius, F. A.: Life Expectancy in Coronary Thrombosis, *J. A. M. A.* **106**:1890 (May 30) 1936.

19. Vander Veer, J. B., and Brown, L. E.: The Diagnosis and Prognosis of Coronary Occlusion: The Electrocardiogram as an Aid, *Pennsylvania M. J.* **39**: 303 (Feb.) 1936.

20. Stroud, W. D., in discussion on Levine, S. A., and Levine, H. D.: Electrocardiographic Study of Lead IV with Special Reference to Findings in Angina Pectoris, *Tr. A. Am. Physicians* **50**:303, 1935.

21. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observation on the Use of Chest Leads, *Arch. Int. Med.* **52**:752 (Nov.) 1933.

From our data it would appear, however, that anterior infarcts are somewhat more frequent than posterior lesions in initial attacks. Here, again, our method of selection may account for the apparent disagreement with the conclusion of Barnes and Ball,²² who dealt with unselected autopsy material, and of Master and associates¹⁴ that the frequency of infarction of the two locations is apparently equal.

The smaller groups based on other electrocardiographic changes make up the remainder of the entire series. Bundle branch block occurred in 9 patients, with a mortality of 78 per cent. Master and co-workers²³ found a similar higher mortality among patients with such a lesion as compared with the mortality among those with normal intraventricular conduction. There were 7 instances of partial or complete heart block or both, in 43 per cent of which the outcome was fatal. Low voltage of the ventricular complexes with no other changes and defective intraventricular conduction with no accompanying alterations each appeared 3 times, with no fatalities. Twelve patients fell into the unclassified group, with a single death for a mortality of 8 per cent. Among them were included those whose electrocardiograms showed no significant changes or only minor abnormalities that could not be helpful in diagnosis. It is interesting that 1 such patient died of a rupture of the area of infarction on the third day, and yet no significant abnormalities of the ventricular complex had been shown in two tracings taken on the first and on the third day. Although these groups are small, it would appear that in general those patients with less striking electrocardiographic changes have a distinctly better outlook, for there was only 1 death among 18 patients in groups 5, 6 and 7 (table 1). In our single case of right ventricular infarction the diagnosis was made at autopsy.

Throughout this study, in analysis of the different clinical features, the influence of various electrocardiographic changes, especially those which differentiate anterior and posterior infarctions, was evaluated. There was one other alteration in the electrocardiogram which we thought worth while to investigate, i. e., the low voltage of the QRS complex in the standard three leads. Wearn^{5b} was among the first to call attention to this alteration in cases of acute coronary thrombosis. Barnes²⁴ reported that this change was encountered twice as often in

22. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am. J. M. Sc.* **183**:215 (Feb.) 1932.

23. Master, A. M.; Dack, S., and Jaffe, H. L.: Bundle Branch Block and Intraventricular Block in Acute Coronary Artery Occlusion, *Am. Heart J.* **16**: 283 (Sept.) 1938.

24. Barnes, A. R.: Electrocardiogram in Myocardial Infarction: A Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, *Arch. Int. Med.* **55**:457 (March) 1935.

patients who died of coronary occlusion as it was in those who recovered and that its presence rendered the prognosis more grave. In our analysis, dealing solely with patients having their initial myocardial infarction, this was not the case. In the entire series, this change in the electrocardiogram was present in 26 per cent of all patients. It was much more common in those who had had no previous hypertension. Of the 54 patients who had a low voltage, 22 per cent died, as compared with a mortality of 35 per cent in 150 patients whose electrocardiograms did not show this change. It would thus appear that the presence of a low voltage of the QRS complex in the electrocardiograms of patients undergoing their first episode of acute coronary thrombosis tends to make the outlook somewhat more favorable.

SEX

Of the entire series of 208 patients, 69 per cent (143) were male and 31 per cent (65) were female. This ratio, with the obvious male predominance, is in accord with that in most large series of patients with coronary occlusion.²⁵ The higher percentage of men was somewhat more striking in the group with posterior infarction (78 per cent) and in the smaller group with partial and complete block (86 per cent). On the other hand, the mortality for all men was 31 per cent, as compared with 35 per cent for all the women. This disparity in male and female mortality rates was almost equally evident in the case of anterior and of posterior infarction. The trend toward a graver prognosis for women may well be accounted for by two factors, which will be discussed later: 1. The average age of women at the time of their first attack tends to be higher. 2. A greater number of women have a history of hypertension antedating the occurrence of myocardial infarction.

AGE

The average age for the entire series was 58.7 years. For the men the average was 57.4 years, while for the women it was 61.5 years. These findings are in accord with previous reports.²⁶ It was observed that 70.5 per cent of all patients fell into the age period between 50 and 69. However, the largest percentage of men in any single decade was 38 per cent, in the 50 to 59 year age period. Women, on the other hand, showed a definite predominance in the 60 to 69 year age period, into which 47 per cent of all patients fell. The fact that a greater proportion of women with coronary occlusion fall into the later period has been observed by Willius¹⁸ and by Conner and Holt.¹⁵ Here it is seen to hold true, even when one is dealing solely with patients having their first attack.

25. Levine.¹⁰ Master, Jaffe and Dack.¹⁴ Conner and Holt.¹⁵ Willius.¹⁸

26. Levine.¹⁰ Master, Jaffe and Dack.¹⁴ Conner and Holt.¹⁵

The average age of those patients that died was 60.8 years, which was definitely higher than that of those who lived, 57.6 years. This difference was true for patients of both sexes. The average age of the men who died was 59.6 years, as contrasted with 56.3 years for those who lived. The average for the women who died was 63.3 years, while for those who survived it was 60.6 years. Even more significant was the fact that the mortality in each decade rose progressively as the older decades were reached, with the exception of that of 30 to 39 years, in which the total number of patients was too small to be evaluated. Thus the patients in the decades from 40 to 49 and 50 to 59 had a mortality of 25 per cent, while 36 per cent of those from 60 to 69 and 50 per cent of those from 70 to 89 died. Previous authors²⁷ have also noted that the younger patients withstand cardiac infarction better than do the older ones.

It is noteworthy that the average ages of the patients in the groups with anterior and with posterior infarction were nearly identical. The distribution over the various decades was alike in the two groups, there being the same proportion of anterior to posterior lesions in those patients under 59 years as in those over 59. The greater age of the women and the higher mortality in the older age ranges were noted equally in the two groups. The foregoing generalizations were true as well in the smaller groups of patients showing other electrocardiographic patterns.

We may conclude that, in general, women are 4 years older than men at the time of the initial acute attack, that for both sexes the mortality increases with advancing years and that these statements are true whether the infarction be anterior or posterior.

PREVIOUS ANGINA PECTORIS

It has long been known that angina pectoris often precedes myocardial infarction.²⁸ In this series, antecedent angina pectoris or its equivalent was present in 71.6 per cent of all patients. It was equally common in men and in women. It was noted just as frequently in patients who had anterior infarction as in those who had posterior infarction. It was found somewhat more often in those with bundle

27. (a) King, H. C.: Prognosis in Coronary Heart Disease and After Coronary Occlusion, *Ohio State M. J.* **33**:524 (May) 1937. (b) Master, Jaffe and Dack.¹⁴ (c) Conner and Holt.¹⁵ (d) Cooksey.¹⁷

28. (a) Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, *Lancet* **1**:4 (Jan. 7) 1928. (b) Smith, F. M.; Rathe, H. W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, *J. A. M. A.* **105**:2 (July 6) 1935. (c) Levine.¹⁰ (d) Howard.¹³ (e) Conner and Holt.¹⁵ (f) Willius.¹⁸

branch block or with defective intraventricular conduction. It tended to be more frequent in our series than in those previously reported, but this may well be explained by the fact that our patients were hospitalized and thus it was possible to obtain a more detailed and exhaustive history. White²⁹ and Bedford³⁰ found that the previous existence of angina pectoris or its duration prior to the attack had no influence on the prognosis of coronary thrombosis. The striking feature here is that the mortality of those patients with previous angina pectoris was only 29 per cent, as contrasted with that of 38 per cent for all patients without antecedent pain. Here, again, the differences were the same in the groups with anterior and with posterior lesions. This would seem to indicate that those patients with previous angina pectoris actually do a little better and that there is possibly some truth in the old clinical impression that those without antecedent pain are caught unprepared with less adequate collateral circulation and succumb more easily.

PREVIOUS HYPERTENSION

Reports in the literature regarding the frequency of hypertension antedating coronary occlusion are not entirely in agreement. Master and co-workers¹⁴ found preexisting hypertension in 66 per cent of their series. It was present in 34 per cent of Conner and Holt's¹⁵ series. Howard¹³ observed it in 28 per cent of his cases. There were 58 hypertensive patients in Levine's¹⁰ series of 145, though information on previous blood pressures was not entirely complete. In our series we have used the criterion of 150 mm. of mercury systolic and (or) 100 mm. of mercury diastolic. The blood pressure readings used under this criterion were those observed or reported prior to the attack in many instances; in others the blood pressure on admission was used, if it was still high and if the patient entered the hospital within a short time after the onset. If the data were inadequate, the case was not included in this analysis. Hypertension existing before the first attack of coronary thrombosis was recorded in 57 per cent of 197 patients for whom pressure readings were known. Interestingly enough, it was far more common in women (86 per cent) than in men (44 per cent). Previous hypertension was equally common in the group with anterior and in that with posterior infarction. Although they form only a small group, it is worthy to note that all the patients with bundle branch block had previous hypertension, a finding similar to one previously reported.²³

29. White, P. D.: The Prognosis of Angina Pectoris and Coronary Thrombosis, *J. A. M. A.* **87**:1525 (Nov. 6) 1926.

30. Bedford, D. E.: Prognosis in Coronary Thrombosis, *Lancet* **1**:223 (Jan. 26) 1935.

It was the impression of Vander Veer and Brown¹⁹ and Bedford²⁰ that the mortality is no higher in the group with hypertension than in the group without, although Master and associates³¹ found a higher mortality in those with previous hypertension. Our findings are in accord with the latter observation. The mortality for those patients with previous hypertension was 36 per cent, as contrasted with a rate of 24 per cent for those with a previously normal blood pressure.

An interesting side light which developed in this analysis, and which is in agreement with the observations of Eppinger and Levine,³² was that of 59 women for whom adequate data were available, only 2 (3.4 per cent) had had neither angina pectoris nor hypertension before the initial attack of coronary thrombosis. On the other hand, of 137 men, 25 (18.2 per cent) had had neither prior to their cardiac infarction. As a corollary of these observations regarding both previous angina pectoris and previous hypertension, it was seen that of patients with the four possible combinations of these two characteristics, those who did the poorest were the patients who had been hypertensive but had had no cardiac pain.

From the foregoing statements it follows that previous hypertension occurs in slightly more than the majority of patients, that hypertension is much more common in women and that the immediate mortality is distinctly greater among hypertensive patients. The combination of absence of antecedent angina and absence of hypertension is extremely rare in women. Finally, the presence of previous hypertension without previous angina is associated with a particularly high mortality. These generalizations were valid whether the infarct was located anteriorly or posteriorly.

BLOOD PRESSURE

A fall in the blood pressure is such a common concomitant of acute myocardial infarction that it has become one of the observations sought for most frequently at the bedside when the diagnosis of such a condition is suspected. In our series there were 170 patients for whom the data regarding changes in blood pressure were felt to be adequate. Here, again, as in the analysis of other features in this investigation, the changes in pressure during the early hours or days were studied, exclusive of the terminal fall in pressure that obviously occurs in most cases of fatal termination.

31. Master, A. M.; Dack, S., and Jaffe, H. L.: *Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis*, *Am. Heart J.* **13**:330 (March) 1937.

32. Eppinger, E. C., and Levine, S. A.: *Angina Pectoris: Some Considerations with Special Reference to Prognosis*, *Arch. Int. Med.* **53**:120 (Jan.) 1934.

In the group of 170 patients, an appreciable drop (20 mm. of mercury or more) in systolic pressure occurred in 68 per cent, while in 32 per cent there was no appreciable fall (less than 20 mm. of mercury). The former group was made up of 88 patients who had previous hypertension and 27 who had previous normal pressure. With 1 exception, all those whose pressure showed no significant fall had previous normal pressures. The mortality among those patients showing a definite fall in blood pressure was somewhat higher (30 per cent) than among those who did not demonstrate such a change (24 per cent).

On a closer analysis of cases in which there was an appreciable fall in systolic pressure, it was observed that in patients who had previous hypertension, the average greatest fall in pressure was somewhat higher among those who died (71 mm. of mercury) than among those who recovered (59 mm. of mercury). In those with previous normal pressures, the average fall in the systolic level appeared to be the same (about 38 mm. of mercury) whether the patient died or recovered. It was noted, however, that many patients with previous hypertension were able to tolerate a drop in systolic pressure as great as 75 to 110 mm. whereas others who died showed a fall of much less extent. It would appear, therefore, that the actual degree of fall in systolic pressure is not of great prognostic significance. However, it was our distinct impression that when the pressure was maintained at a level below 80 mm. systolic for many hours or days the outlook became unfavorable. A similar belief was expressed by Middleton³³ and by Bedford.³⁰

A study was also based on the lowest pulse pressure observed during the course of the patient's illness. Master and his co-workers³¹ reported a mortality of 58 per cent in patients with pulse pressures of 20 mm. or less, as compared with 14 per cent in those with pulse pressures of 30 mm. or more. In our series, the result has been much the same, there being a mortality of 54 per cent in those whose lowest pulse pressure was less than 20 mm. and of 30 per cent in all those whose lowest pulse pressure was above that level. This fact was true regardless of the electrocardiographic pattern.

Wood and associates²¹ noted that in some cases of acute coronary thrombosis the blood pressure did not begin to drop until twelve hours after the initial symptoms appeared. Fishberg and his co-workers³⁴ noted that in some cases the blood pressure may actually rise for a time. They expressed the belief that this occurred when failure of the

33. Middleton, W. S.: The Prognosis and Treatment of Coronary Occlusion, *Minnesota Med.* **18**:710 (Nov.) 1935.

34. Fishberg, A. M.; Hitzig, W. M., and King, T. H.: Circulatory Dynamics in Myocardial Infarction, *Arch. Int. Med.* **54**:997 (Dec.) 1934.

left ventricle was severe enough to produce outspoken pulmonary edema and that it was largely a consequence of asphyxia. In this series there were 10 patients for whom the data available were complete enough for it to be said with certainty that a rise in the blood pressure level accompanied the onset of myocardial infarction, the customary fall then occurring after some hours or days. Three of these patients had had previous hypertension, while in the others the previous levels had been normal. In the majority the rise in blood pressure was observed while the patient was suffering from pain, but this was not always the case. In 2 patients, 1 of whom was previously hypertensive, the highest blood pressure level was observed three days after the onset of symptoms. In only 1 case was this phenomenon associated with acute pulmonary edema. Four patients had anterior infarcts, 3 had a posterior lesion, 1 had defective intraventricular conduction and the remaining 2 fell into the unclassified group. It is also worth while to note that all of these patients recovered. The mechanism of this temporary rise in blood pressure is not clear. In a study of patients with angina pectoris, Levine and Ernstene³⁵ concluded that pain alone as a stimulus was not sufficient to cause the elevation of blood pressure during attacks of cardiac pain. Whatever the explanation for this phenomenon may be, it is well to remember that it can occur, and the diagnosis should not be ruled out because of an initial rise or a failure of the blood pressure to fall during the first few hours or days following acute myocardial infarction.

PAIN

Pain is perhaps the symptom most commonly found in patients with myocardial infarction. It is well recognized that its severity and location vary greatly from patient to patient. It seemed worth while to analyze this feature in detail to determine any prognostic significance it might have. In order to do this the pain, as experienced by each patient, was classified as absent, mild, moderate or severe, depending on its intensity and duration. Again the cases were grouped, as in each analysis in this study, according to the electrocardiographic findings.

Previous observers³⁶ have expressed the belief that the severity of the pain during the attack had little influence on the outcome. Middleton³³ has found that some of the most ominous attacks are either mild or free from pain. On the whole, the results of our studies are in agreement with this point of view. There was no constant relation between the intensity of the pain and the prognosis, as was demon-

35. Levine, S. A., and Ernstene, A. C.: Observations on Arterial Blood Pressure During Attacks of Angina Pectoris, *Am. Heart J.* 8:323 (Feb.) 1933.

36. Willius.¹⁸ Bedford.³⁰

strated by the fact that of 46 patients with pain of mild degree 39 per cent died, of 110 patients with moderately severe pain 24 per cent died and of 47 with severe pain 43 per cent died. This conclusion is further borne out by the evidence that of 6 patients with no pain at all 5 died. Moreover, the average degree of pain for each of the various groups was nearly the same. The only exception to this was that patients with posterior infarction tended to have slightly less severe pain than those with anterior infarction.

The literature contains occasional comments²¹ regarding the distribution of the pain as a guide to the location of the infarction. In this series 93 per cent of all patients had pain or similar feelings of distress, like constriction, burning or pressure, in some area of the chest; in 19 per cent there was radiation to the right arm (in all but 1 case there was also radiation to the left arm); in 48 per cent there was radiation to the left arm; in 14 per cent the discomfort was partially or wholly in the upper part of the abdomen, and in 16 per cent the distress radiated to the back. In one third of the patients the pain was experienced solely in the chest; 1, and possibly a second, patient had discomfort only in the left arm and shoulder, and in 5 patients the pain was entirely abdominal. None of the patients experienced distress solely in the right arm or in the back. Only 1 patient had thoracic pain with radiation to the right arm alone, whereas 47 patients (23 per cent) had thoracic pain with radiation to the left arm alone. Some patients with bilateral radiation had more marked discomfort in the right arm. For the most part, the site and the distribution of the pain appeared to play no role in the outcome, nor was there any definite relation to the electrocardiographic findings. Notable exceptions were as follows: First, patients with no thoracic pain at all had a higher mortality than those with such pain (11 deaths among 15 patients, i. e., 73 per cent, as compared with 56 deaths among 191 patients, i. e., 29 per cent). Second, patients with anterior infarction and pain radiating to the left arm did better than those with a lesion in the same location but without such distribution of pain (11 deaths among 55 patients, i. e., 20 per cent, as compared with 22 deaths among 54 patients, i. e., 41 per cent). Last, radiation of pain to the right arm was somewhat more frequent in patients with posterior infarction than in those with anterior infarction (17 of 64 patients, i. e., 22 per cent, as compared with 17 of 109 patients, i. e., 16 per cent).

As Levine and Tranter^{5a} first pointed out in 1918, in some patients with coronary thrombosis the pain is localized wholly to the upper part of the abdomen. Five patients in our series fell into this category. Of this number, there were 3 with anterior infarction, all of whom died, the diagnosis being confirmed by postmortem examination in the 1

instance in which autopsy was permitted. There were 1 patient with a posterior infarct and 1 in the unclassified group; both these patients survived.

Of the entire group of 208 patients, there were 4 who had no pain or sense of oppression at all and 2 more in whom pain was thought to be absent but whose history was not satisfactory. Thus, at most, 3 per cent of the patients had "painless myocardial infarction." This finding corroborates those of Pollard and Harvill³⁷ and Kennedy,³⁸ although it is a far smaller percentage than that reported by Gorham and Martin.³⁹ Of these 6 patients, 4 had an anterior and 2 a posterior infarct. All of the former and 1 of the latter succumbed, the diagnosis and the location of the lesion being confirmed at autopsy in all cases.

We may summarize by stating that the severity and distribution of the pain were of little value in estimating the prognosis or in predicting the location of the infarction. It was also found that "painless" infarction is rare (3 per cent), that localization of pain of the upper part of the abdomen is also rare (2.4 per cent) and that although the numbers of patients with either condition may be small, the mortality may possibly be higher than the average.

DYSPNEA

As most clinicians are well aware, dyspnea may play a prominent role in the symptomatology of myocardial infarction. Perhaps because it is a more disagreeable sensation, the patient's attention is usually directed toward his pain. If he is questioned and observed closely, however, shortness of breath of varying degrees will be found in the majority of instances. In some cases extreme dyspnea may be the only complaint. Furthermore, as Christian⁹ and Levine¹⁰ have pointed out, there is frequently a disproportion between the degree of dyspnea and any abnormalities demonstrable in the heart or lungs. Bedford³⁰ has indicated that severe dyspnea is an unfavorable sign in coronary thrombosis.

In order to determine the value of this complaint as a prognostic indication the intensity of dyspnea presented by each patient was classified as absent, mild, moderate or severe. From this analysis it was learned that the patients who survived had definitely less dyspnea than those

37. Pollard, H. M., and Harvill, T. H.: Painless Myocardial Infarction, *Am. J. M. Sc.* **199**:628 (May) 1940.

38. Kennedy, J. A.: The Incidence of Myocardial Infarction Without Pain in Two Hundred Autopsied Cases, *Am. Heart J.* **14**:703 (Dec.) 1937.

39. Gorham, L. W., and Martin, S. J.: Coronary Artery Occlusion With and Without Pain: An Analysis of One Hundred Autopsied Cases with Reference to the Tension Factor in Cardiac Pain, *Tr. A. Am. Physicians* **53**:129, 1938.

who died. Furthermore, the average degree of dyspnea in patients with anterior and that in patients with posterior infarction were almost identical. Patients with bundle branch block had slightly more dyspnea, on the whole, than did those in other electrocardiographic groups, a feature which corresponds with the higher mortality among those with this type of lesion.

In summary, it was seen that in 29 per cent of the patients dyspnea was absent, in 24 per cent it was mild, in 28 per cent it was moderate and in 19 per cent it was severe. In a consideration of mortality, it was found that of 140 patients who recovered there were 63 per cent with no or mild dyspnea and 37 per cent with moderate or severe dyspnea whereas the corresponding figures for 68 patients who died were 34 and 66 per cent, respectively. This relation is further emphasized by the relative mortality for the four degrees of dyspnea (table 2). It was also noted that each of the 6 patients with myocardial infarction without pain had either moderate or severe dyspnea. Therefore this

TABLE 2.—*Significance of Dyspnea in Two Hundred and Eight Patients with Acute Myocardial Infarction*

Degree of Dyspnea	Number of Patients	Number of Deaths	Mortality, Percentage
Absent.....	61	11	18
Mild.....	50	12	24
Moderate.....	58	21	36
Severe.....	39	24	62

feature can serve not only as a key to prognosis but, in some cases, as an aid in diagnosis. It would appear, then, that the degree of dyspnea is a far more reliable indication of the patient's outlook than is the severity of pain.

SWEATING

In many cases patients who suffer from acute coronary occlusion will state that at the onset they "broke out in a cold sweat." In others, the skin on first examination will be found to be excessively moist. In fact, some patients will have a moist skin for many days or weeks after the onset. The frequent occurrence of sweating is indicated by the fact that it was present in 70 per cent of the patients. It was seen slightly more often in those who died, but the very fact that it is so common lessens its prognostic importance. It is our impression, however, that a patient should be given a more guarded prognosis if his skin remains excessively moist over a period of several days after the onset or if he begins to manifest this characteristic after having been doing well.

CYANOSIS

Cyanosis is observed in a large proportion of persons suffering from myocardial infarction. In this series it was found in slightly over half of all the patients. In the study of Master and co-workers,³¹ 29 per cent of those who died showed it, while only 9 per cent of those without it failed to recover. In our series, the mortality of those with cyanosis was 45 per cent, as contrasted with a mortality of 16 per cent for those without it. Cyanosis appeared with equal frequency and was of the same import in patients with anterior and in those with posterior lesions.

SHOCK

The patient who is suffering from acute myocardial infarction often presents the picture of shock. Fishberg, Hitzig and King³⁴ demonstrated that in persons undergoing their initial myocardial infarction the venous pressure and the circulating blood volume both tend to be those characteristic of shock. Other observers⁴⁰ have found that the appearance of peripheral circulatory collapse makes the prognosis more grave.

As with the manifestations of pain and dyspnea, the evidences of shock demonstrable for each patient in this series were classified as absent, mild, moderate or severe. Some degree of shock was present in 54 per cent of 205 patients. The mortality of those with shock was 44 per cent and for those without shock 28 per cent. The average degree of shock in those who died was definitely greater than in those who recovered. The mortality increased noticeably with higher degrees of shock, as the following figures show: absence of shock (95 patients), 20 per cent died; mild shock (57 patients), 26 per cent died; moderate shock (39 patients), 51 per cent died, and severe shock (14 patients), 93 per cent died. It was slightly greater in those with bundle branch block and those with partial or complete heart block than in those with other disturbances. There was a larger percentage of patients with posterior infarction who had severe shock than of those with anterior infarction. In judging the prognostic value of the degree of shock, the electrocardiographic changes afforded no additional aid.

CHARACTER OF HEART SOUNDS

Auscultation is usually more fruitful in cases of acute myocardial infarction than in cases of other forms of coronary arterial disease. Pericardial friction, gallop rhythm, various arrhythmias and the general quality of the heart sounds are all important signs for which search should be made. Gallop rhythm was present in 20 per cent of all

40. Levine.¹⁰ Master, Dack and Jaffe.³¹

patients in this series. The mortality rate among patients with gallop rhythm was 43 per cent, as contrasted with that of 29 per cent for those without it, a result agreeing with the observation of Master and associates.³¹ This abnormality appeared less frequently in patients with posterior infarction (13 per cent) than in those with an anterior lesion (22 per cent). However, when it did occur, it had a greater prognostic significance for patients with a posterior lesion than for those with an anterior lesion, the respective mortality figures being 62 and 33 per cent. As was to be expected, gallop rhythm was found in three fourths of the patients with bundle branch block.

The heart sounds were described as faint or muffled in 60 per cent of all patients. This abnormality also carries some prognostic import, for the mortality was 38 per cent in those who showed it as compared with 25 per cent in those who did not. This confirms the impression expressed by Middleton.³³ It occurred with equal frequency in association with anterior and with posterior infarction.

Auscultation over the precordial area in a patient who has suffered an acute myocardial infarction will often reveal a pericardial friction rub. This sign is often only transient, so that in some instances it will be missed unless frequent examinations are carried out. A search of the literature⁴¹ for figures regarding the frequency with which a pericardial friction rub is heard after cardiac infarction yielded results ranging from 7 to 42 per cent. In our series there were 206 patients for whom the examination was considered adequate, and of these a pericardial friction rub was demonstrable in 16 per cent, usually some time during the first week after the initial symptoms of the attack. Previous reports are not in agreement as to the significance of a pericardial friction rub. Some authors⁴² have expressed the belief that it did not influence the prognosis; others²⁹ have indicated that it occurred more commonly in those patients who died. In this series of patients, who were undergoing their initial attack of myocardial infarction, the mortality was 45 per cent for those in whom a friction rub was heard, while it was 31 per cent for those in whom this sign was absent.

Riseman and Harris⁴³ pointed out that pericardial friction can be detected, particularly when the infarcted area is located anteriorly. Of the 7 patients whose cases they reported, Vander Veer and Brown¹⁹ observed this sign in 4 with anterior infarct and in 3 with a posterior

41. Coombs, C., and Ryle, J. A.; in discussion on Cardiac Infarction, *Lancet* 1:189 (Jan. 28) 1928. Howard.¹³ Vander Veer and Brown.¹⁹ Parkinson and Bedford.^{28a}

42. Bedford.³⁰ Middleton.³³

43. Riseman, D., and Harris, S. E.: Diseases of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease, *Am. J. M. Sc.* 187:1 (Jan.) 1934.

lesion. In our series of 33 patients who showed this abnormality, 28 had an infarction of the anterior portion of the left ventricle and 5 had a posterior lesion. Of the latter, 2 were examined post mortem. In both the antemortem localization of the infarct was confirmed. One of them had a terminal rupture of the posterior infarct. Thus, it may be said that although it is far more common in conjunction with anterior infarction, pericardial friction may be heard in patients who have suffered a posterior infarct and that this physical finding, of itself, does not localize the infarction. In addition, there were 4 patients in whom definite pericarditis was found post mortem but who had shown no pericardial friction. It is possible that the rub was overlooked or was too faint or too indistinct to be clearly distinguished.

It seems reasonable to state that the presence of pericardial friction indicates a significant area of myocardial infarction and in that sense would be accompanied by a somewhat graver prognosis than exists in many cases of the milder forms in which the area of involvement is smaller and does not reach the pericardial surface. However, a comparison of patients who are equally sick in other respects suggests that the presence of a friction rub probably has no significant effect on the outcome.

TEMPERATURE

It is a well recognized fact that fever of moderate degree usually appears in the course of myocardial infarction. The analyses of King,^{27a} Master and co-workers³¹ and Middleton³³ have indicated that if the fever is of high degree and long duration the outlook becomes unfavorable. Use of the highest rectal temperature not attributable to a complication during the course of the disease gave a similar result in the study of our patients with regard to fever. Rectal temperatures of 100 F. or more were observed in 93 per cent of all patients. In 84 per cent the highest temperatures fell between 100 and 102.9 F. In 6 instances the rise of temperature to levels of 104 F. or over was due solely to the cardiac lesion.

Among those patients who were observed during the first week of their illness, there were 10 whose rectal temperature never rose to 100 F. In fact, there were 3 whose rectal temperature did not reach 99 F., but 2 of these were patients in shock who did not survive long enough for the secondary evidences of infarction to develop. The other definitely had an anterior infarction, with classic electrocardiographic changes but without fever, leukocytosis, fall in blood pressure or any acceleration in the pulse rate. It seemed that some of the patients whose highest temperature ranged from 99 to 100 F. lacked the characteristic sudden onset and behaved as if the occlusion required several days to develop.

The mortality varied directly with the height of the temperature (table 3). For those whose highest temperature fell in the range between 100 and 102.9 F. (172 patients) the mortality was 29 per cent, while it was 64 per cent for those with temperatures between 103 and 103.9 F. (11 patients) and 83 per cent for those with elevations to 104 F. or over (6 patients). It was difficult to analyze the significance of the duration of fever because the time of first observation after the onset varied so much.

PULSE RATE

Conner and Holt¹⁵ used the changes in pulse rate as one of the criteria of the severity of the attack. Master and co-workers³¹ observed a mortality of 44 per cent for those with pulse rates of 120 or over, as contrasted with 10 per cent for those whose rate was never over 100 per minute. We have reviewed the case of each patient in our series for the highest pulse rate observed at any time during the acute phase

TABLE 3.—*Significance of Highest Rectal Temperature in One Hundred and Ninety-Nine Patients with Acute Myocardial Infarction*

Temperature (F.)	Number of Patients	Number of Deaths	Mortality, Percentage
Up to 99.9.....	10*	4†	40
100 to 100.9.....	68	14	21
101 to 101.9.....	54	18	33
102 to 102.9.....	50	18	36
103 to 103.9.....	11	7	64
104 and over.....	6	5	83

* Patients whose temperature fell in this zone were excluded if they were not observed during the first week of disease.

† Three of these 4 deaths were of patients who entered the hospital in severe shock and died within a few hours of the initial symptoms of the attack.

after the attack, excluding so far as possible those changes due to complications or to such arrhythmias as paroxysmal auricular fibrillation, paroxysmal ventricular tachycardia and heart block.

The average highest pulse rate for all patients was found to be 107 per minute. The average for those who survived was 104, as contrasted with 115 for those who died. Patients in whom the infarction involved the anterior wall of the left ventricle tended to have a higher rate than those with a posteriorly placed lesion. This is further brought out by the fact that 22 per cent of those with an anterior lesion had rates between 80 and 99, whereas 39 per cent of those with a posterior lesion fell into this zone. On the other hand, in 27 per cent of those with an anterior lesion the highest pulse rate ranged between 120 and 139, while the corresponding figure for those with a posterior lesion was only 13 per cent. The mortality for the entire series showed a progressive increase as the pulse rate rose, only 7 per cent of those with rates between 80 and 99 dying, as compared with 52 per cent of those

with rates over 120. Furthermore, there was evidence to suggest that when a pulse rate of over 120 is observed in a patient with a posterior infarct, the outlook is even more serious than it is when such a rate is seen in conjunction with an anterior lesion.

A pulse rate between 60 and 80 per minute in the absence of heart block is not incompatible with the presence of a myocardial infarction. Seven instances of such an association were seen in this series. In 1 case the infarction occurred while the patient was in the hospital. At no time was his pulse rate above 68, and an electrocardiogram three days after the acute attack showed evidence of an anterior infarct, with a pulse rate of 47 per minute but without signs of heart block. Such patients possibly have slow heart rates normally.

RESPIRATORY RATE

Analysis of the respiratory rate, the basis being the highest rate attributable to the infarction itself or to the pulmonary congestion resulting from it, gave results in accord on the whole with those of Master and co-workers.³¹ The average highest respiratory rate for those patients who died was higher than that for those who survived. In addition, the mortality tended to rise directly with the respiratory rate. There was no significant variation within the several electrocardiographic groups in this respect. The actual respiratory rate, however, would seem to be of less value than other clinical observations.

LEUKOCYTE COUNT

Levine and Tranter^{5a} and Libman⁴⁴ were among the first to point out the frequent appearance of leukocytosis in conjunction with other manifestations of acute coronary thrombosis. Other workers⁴⁵ have indicated that a high leukocyte count renders the outlook unfavorable. In our series the average highest leukocyte count for all patients was 15,000 per cubic millimeter, and, in addition, the average for those who lived was definitely lower (13,500) than that for those who died (18,800). Patients with anterior infarction tended to have a slightly higher leukocyte count (15,700) than those with a posterior lesion (14,200). Patients showing partial and complete heart block had the highest average leukocyte count (19,200), possibly because they had a larger area of heart muscle involved. The outlook appeared to be progressively more serious as the leukocytosis reached higher and higher levels. Of 118 patients with white blood cell counts under 15,000, only

44. Libman, E.: The Importance of Blood Examinations in the Recognition of Thrombosis of the Coronary Arteries and Its Sequelae, *Am. Heart J.* **1**:121 (Oct.) 1925.

45. King.^{27a} Master, Dack and Jaffe.³¹

16 per cent died, while of 83 with leukocyte counts above that level 54 per cent died. This fact held equally true for each of the electrocardiographic groups. It should be pointed out, furthermore, that 14 per cent of the patients had leukocyte counts below 10,000 during the first week following the initial onset of symptoms, and in 3 per cent the level was over 30,000 at some time in the course of the attack. Thus neither marked leukocytosis nor a normal white cell count is incompatible with the diagnosis of myocardial infarction. Although fever and leukocytosis generally go together, either one may be present in the absence of the other during the first week following an acute attack of coronary thrombosis, and rarely are both absent.

SEDIMENTATION RATE

Among the more recent observations in cases of myocardial infarction has been the frequency with which the sedimentation rate becomes elevated. Rabinowitz and co-workers⁴⁶ were the first to appreciate this change and felt that it might well be a good index of the progress of healing of the area of myelomalacia due to a coronary occlusion. Gorham and Thompson⁴⁷ obtained little information concerning prognosis from the determination of this factor. Unfortunately, the information regarding sedimentation rates in our series was not complete. The test was carried out for one fourth of all patients, but for most of them serial observations were not made. It may be said, however, from the data available that the height of the sedimentation rate would seem to have scant prognostic value. The test occasionally had value as a diagnostic procedure, particularly in cases in which clinical and electrocardiographic findings were equivocal.

CONGESTIVE FAILURE

Pulmonary Congestion and Acute Pulmonary Edema.—Pulmonary congestion is a common concomitant of acute coronary thrombosis. It may range from merely a few rales at the base of the lung to coarse rales throughout the entire pulmonary field, with an associated sense of suffocation on the part of the patient. We have reviewed the cases of our entire series of 206 patients in which the information was complete in this regard and have designated the congestion as one of four degrees: (1) absent (no rales), (2) mild (a few basal rales), (3) moderate (many rales, without respiratory distress) and severe (generalized rales, with suffocation). Only the pulmonary changes present during the first

46. Rabinowitz, M. A.; Shookoff, C., and Douglas, A. H.: Red Cell Sedimentation Time in Coronary Occlusion, *Am. Heart J.* 7:52 (Oct.) 1931.

47. Gorham, L. W., and Thompson, H. C.: A Study of Erythrocyte Sedimentation Rate and Differential Leucocyte Count in Coronary Occlusion, *Internat. Clin.* 1:44 (March) 1938.

day or so were analyzed, as it is obvious that congestion will be extremely common as a terminal manifestation. From this analysis it was learned that the average degree of pulmonary congestion in the patients who died was twice as great as that in those who recovered. With but few minor exceptions, this held true no matter what the electrocardiograms showed. The average degree of pulmonary congestion in patients with anterior infarction and in those with posterior infarction was the same. Patients with bundle branch block had, on the whole, more extensive pulmonary changes than patients in any of the other electrocardiographic groups.

Of the series as a whole, 29 per cent had no evidence of pulmonary congestion, 39 per cent had it to a mild degree, in 15 per cent it was moderate and in 16 per cent it was severe. Among the patients who died, only 9 per cent showed no rales and 55 per cent had moderate or marked evidence of congestion. Of all patients studied, pulmonary congestion was absent most frequently (50 per cent) in those having electrocardiograms of the unclassified type.

TABLE 4.—*Significance of Degree of Pulmonary Congestion in Two Hundred and Six * Patients with Acute Myocardial Infarction*

Degree	Number of Patients	Number of Deaths	Mortality, Percentage
Absent.....	58	6	10
Mild.....	82	25	30
Moderate.....	32	14	44
Severe.....	34	23	68

* Data regarding this point were considered inadequate for 2 patients.

The rather important prognostic significance of the degree of pulmonary congestion was brought out further by the mortality for each of the four degrees (table 4): absent, 10 per cent; mild, 30 per cent; moderate, 44 per cent, and severe, 68 per cent. Here, again, this clinical feature was of nearly the same importance in each electrocardiographic group.

It is not at all uncommon for a person suffering from an acute myocardial infarction to exhibit what is commonly termed acute pulmonary edema or acute left-sided heart failure either at the onset of his attack or during the first few days after the initial symptoms appear. Such persons obviously fall into the group designated in the preceding paragraph as having severe pulmonary congestion. In our series this clinical picture was observed in 13 per cent of all patients. It was equally common in those with an anterior lesion, in those with posterior infarction and in those showing partial and (or) complete heart block. It was far more frequently seen, however, in patients with bundle branch block, being present in over one half. When this clinical phenomenon occurred it was of grave importance inasmuch as it carried

a mortality of 64 per cent, as contrasted with a mortality of 28 per cent for those who did not show it. It was even more serious in the presence of a posterior infarction, for 7 out of 8 patients with that type of lesion and acute pulmonary edema died as compared with 7 among 12 patients with anterior infarction and acute left-sided heart failure.

It is clear from this study that significant pulmonary congestion during the early days after an attack of acute coronary thrombosis materially increases the gravity of the outlook.

Palpable Liver and Peripheral Edema.—It is not uncommon for acute coronary thrombosis to be followed by acute hepatic engorgement, with the result that physical examination within the first few days of illness will reveal a palpable liver. For the most part hepatic enlargement is apt to occur after six to ten days has elapsed. In this series the liver was reported as palpable in 29 per cent of all patients. It is true, however, that in some this physical finding may have been present prior to the acute infarction. Libman⁴⁸ has suggested that enormous acute engorgement of the liver should lead one to suspect thrombosis of the right coronary artery. This supposition was not borne out in our study. Of the 6 patients examined post mortem who showed thrombosis of one of the branches of the right coronary artery 2 had a palpable liver, and of the 23 with involvement of the left coronary artery the liver was felt in 10. In fact, there were some patients with involvement of the left coronary artery observed at autopsy who showed an enlarged liver and who died within the first forty-eight hours. A palpable liver was frequently observed in patients with bundle branch block (5 out of 9) and was slightly more commonly associated with posterior infarction (21 out of 64) than with an anterior lesion (29 out of 108). In the entire series, the finding of a palpable liver proved to be of only slight prognostic value, since the mortality was 40 per cent when it was present and 30 per cent when it was absent.

As is the case with hepatic engorgement, peripheral edema may often make its appearance a few days after the initial manifestations of myocardial infarction. This occurred in 22 per cent of our total of 208 patients. When it did appear it was of some gravity, for the mortality for patients with edema was 50 per cent as compared with that of 28 per cent for patients without edema. As was the case with a palpable liver, peripheral pitting was slightly less commonly associated with anterior infarction (21 per cent) than with a posterior lesion (25 per cent) or with bundle branch block (33 per cent). When it did develop, however, it was of greater significance in patients with anterior infarc-

48. Libman, E.: Some Observations on Thrombosis of Coronary Arteries, Tr. A. Am. Physicians 34:138, 1919.

tion, for 61 per cent of them died as compared with 22 per cent of those with such a lesion but without edema. On the other hand, among patients with posterior infarction, the mortality was only slightly higher (44 per cent) for those with edema than for those without it (33 per cent).

Thus it may be said that, though a palpable liver and (or) peripheral edema are less common in conjunction with anterior infarction than with a posterior lesion or with bundle branch block, when they do occur the outlook is graver for patients with the first condition than for those with either of the last two.

Right and Left Heart Failure.—In our series, some physical signs of congestive failure occurred in 72 per cent of all patients and tended to be somewhat more common and more severe in those who had had previous hypertension. This finding is in accord with the observations of other workers.³¹ It is clear that congestive failure makes the outlook in myocardial infarction more grave, for those who showed evidences of decompensation had a mortality of 41 per cent as contrasted with a mortality of 12 per cent for those who did not. Left heart failure alone occurred in 40 per cent of all patients and carried a mortality of 36 per cent. Right heart failure alone occurred in only 2 patients (1 per cent), both of whom recovered. Right and left heart failure together appeared in 31 per cent of all patients, of whom 49 per cent died.

Pletnew⁴⁹ and Kohan and Bunin⁵⁰ have indicated that right heart failure points to thrombosis in the right coronary arterial system. Fishberg and his co-workers³⁴ have stated that "it has not seemed that the type of circulatory failure present permits, of itself, the differentiation between right and left coronary occlusion." On the whole, our findings have been in agreement with the latter view. Considering left heart failure alone, we found it occurred slightly more commonly in association with anterior infarction (44 per cent) and with partial or complete block (57 per cent) than with posterior infarction (35 per cent) or with bundle branch block (33 per cent). However, when it did occur, it rendered the prognosis somewhat more serious for the patients with a posterior lesion, for 48 per cent of them died as compared with 42 per cent of those with an anterior lesion. Right heart failure alone developed in only 2 patients, both of whom had posterior infarction and both of whom survived. Right and left heart failure together occurred with almost the same frequency in patients with anterior infarction (31 per

49. Pletnew, D.: Zur Frage der intravitalen Differentialdiagnose der rechten und linken Coronararterienthrombose des Herzens, *Ztschr. f. klin. Med.* **102**:295, 1926.

50. Kohan, B. A., and Bunin, E. I.: Zur Frage über die Differentialdiagnose der Thrombose der rechten und der linken Kranzarterie des Herzens am Lebenden, *Ztschr. f. Kreislaufforsch.* **20**:199 (April) 1928.

cent) as in those with a posterior lesion (32 per cent). It was more commonly seen in patients with bundle branch block (55 per cent). Decompensation of this type had a somewhat greater significance in patients with an anterior lesion, for 52 per cent of them died as compared with 45 per cent of those with a posterior lesion and both right and left heart failure.

Fishberg and associates⁵¹ expressed the opinion that severe right heart failure pointed to involvement of the intraventricular septum by the infarction. In our series, 36 patients were examined post mortem. (In 1 additional patient the statement regarding the septum was inadequate.) Of 20 patients with right and left heart failure, 14 had septal involvement and 6 did not. In 13 patients with left heart failure alone, 7 showed extension to the septum, whereas it was absent in 6. Three patients died without showing any clinical evidence of congestive failure; 2 of them were found to have areas of infarction which included portions of the septum. It may be said, then, that although the development of right and left heart failure may suggest involvement of the septum, the relation is not close enough to be clearly diagnostic.

From the foregoing data it follows that some form of congestion, especially that of the left ventricle, occurred in about three fourths of the patients and was more common in those with hypertension. Early pulmonary congestion was least frequent in the patients who recovered, and the mortality increased progressively with the more severe degree of congestion. The location of the infarct either anteriorly or posteriorly did not influence the degree of pulmonary congestion. Failure of the right side of the heart as evidenced by a palpable liver and by peripheral edema was slightly more commonly associated with posterior than with anterior infarction, but when it did occur, the outlook was more grave for the patients with an anterior lesion.

COMPLICATIONS

The progress of a patient who has suffered an acute myocardial infarction may at any time become complicated by any one of a number of grave situations. They play no small part in rendering the disease as serious as it is. In this study we have included in the mortality statistics those patients in whom the picture was complicated by intercurrent disease or by situations which we feel would not have supervened had the patient not had the original acute coronary thrombosis. The incidence and significance of the more common and important complications will be discussed.

51. Padilla, T., and Cossio, P.: Pronóstico del infarto de miocardio. *Rev. argent. de cardiología*. 1:181 (July-Aug.) 1934.

Pulmonary infarction occurred in 8 per cent of all patients, with a mortality of 53 per cent, as compared with that of 31 per cent for those patients showing no evidence of this complication. It is well recognized that intramural thrombi frequently form over the endocardium of an area of cardiac infarction. Since infarction almost always occurs in the left ventricle, a thrombus can form in the right ventricle only if there is extension to the interventricular septum or to the myocardium of the right ventricle. Such a thrombus can then serve as the source for pulmonary emboli. Of the 9 patients in our series who died after an illness complicated by pulmonary infarction, 8 were examined post mortem. Of these, only 2 showed a thrombus over the right surface of the interventricular septum. A third patient had an infarct which involved only the right anterior ventricular wall, and a large intramural thrombus was found over it. This patient showed thrombosis of the right coronary artery. In the remaining 5 patients no source of pulmonary emboli could be found in the heart. It is well known that two other mechanisms are commonly responsible for pulmonary infarction in cardiac disease, i. e., local thromboses of pulmonary vessels and phlebitis with thrombosis of the veins of the pelvis and legs. These two mechanisms very likely explain the infarction in the aforementioned 5 patients.

Such factors as the advanced age of many of the patients, the enforced rest in bed, the pulmonary congestion and the sedation and narcosis necessary for relief of distress may lead to the development of pneumonia in persons who have had acute coronary thrombosis. In our series, this complication arose in 9 per cent of the patients. Its grave significance is indicated by the fact that 89 per cent of those in whom it appeared succumbed. It was equally common in patients with anterior and in those with posterior infarction.

The course of many patients with acute myocardial infarction is complicated by the appearance of a psychic disturbance, a hallucinatory or delusional state. Such mental disturbances occurred in 7 per cent of all patients in this series. Levine¹⁰ and Middleton³³ have reported that such a development renders the outlook less favorable. This was confirmed in our series, for those patients whose course was complicated in such a manner had a mortality of 60 per cent, as compared with a mortality of 31 per cent for those who showed no disturbance in the psyche.

Cerebral vascular accidents constitute another complication. They may result from cerebral hemorrhage, cerebral thrombosis or cerebral embolism. There were 9 patients in this series who showed evidence of cerebral vascular accident. Seven of them succumbed, an indication of the gravity which obtains in such a complication. Because

of the great frequency of intramural thrombus formation in the left ventricle over the infarcted area, a cerebral embolism is a particular hazard. Of the 37 patients who were examined post mortem, 14 showed a left ventricular mural thrombus, and in 3 of these there was also a thrombus in the right ventricle. One additional patient showed only a right ventricular mural thrombus. There were 3 patients with an auricular thrombus, none of whom had valvular disease; 2 of them are included with the aforementioned 14 patients with left ventricular thrombi, and the third had no other thrombi.

Other complications which would appear to make the outlook more serious include renal infarction, which occurred in 3 patients, with 2 deaths, and splenic infarction, which developed in 6 patients, with 5 deaths. Embolism of the arteries of the limbs seems to be less frequent, as in only 1 case was this recognized clinically. Of the 37 patients post-mortem examination of whom was permitted, a myocardial rupture, occurring three and a half, eleven and fifteen days, respectively, after the onset, was demonstrated in 3. In 1 case a clinical diagnosis of ruptured intraventricular septum was made in a patient who had an anterior infarction and in whom while in the ward a loud systolic murmur developed. This patient died, but permission for autopsy was not granted. Although sudden death during acute coronary thrombosis is often due to a rupture of the ventricle, this is not always the case. There were several cases in which death came abruptly, in 2 of which no rupture could be found on postmortem examination. Such instantaneous fatalities may occur during the first week or so after the onset of the attack, even when the patient seems to be doing well. In some, but not all, instances of sudden death not due to rupture, an antecedent heart block may have been present.

Six patients of the entire series showed definite evidence of valvular heart disease. Two of them had aortic stenosis; both died, and the diagnosis was confirmed at autopsy for the 1 for whom postmortem examination was allowed. Two patients had mitral stenosis and insufficiency; 1 of them succumbed, and postmortem examination confirmed the diagnosis. One patient had both mitral stenosis and insufficiency and aortic stenosis and insufficiency. He had a myocardial infarction at the age of 39 and recovered satisfactorily. One patient had syphilitic aortic insufficiency and recovered, despite an onset characterized by both acute pulmonary edema and paroxysmal auricular fibrillation. It would appear from even this small number of patients that acute coronary thrombosis does occur in the presence of valvular disease and that the outlook for recovery of patients with such a condition is approximately 50 per cent.

ARRHYTHMIAS

Abnormalities of the cardiac rhythm occur with great frequency during acute coronary thrombosis. These are of a wide variety, and it will be our purpose here to discuss only the major disturbances observed in this series. Of all the patients, 38 per cent showed some arrhythmia. In many instances the same patient showed two or three different types of deranged cardiac mechanisms at different times. Patients who showed some disturbance of cardiac rhythm had a mortality of 42 per cent, as compared with a mortality of 27 per cent for those who did not, a finding which is in agreement with the observations of Middleton,⁵³ Padilla and Cossio⁵¹ and Master, Dack and Jaffe.⁵²

The analysis of the cases of those patients who showed auricular fibrillation was particularly interesting. Levine¹⁰ has pointed out that patients with persistent auricular fibrillation rarely have subsequent myocardial infarction. He reported that its occurrence during a myocardial infarction does not appreciably alter the prognosis and that, though usually transient, the fibrillation may persist after recovery. In this series auricular fibrillation occurred in 25 patients (12 per cent). Its presence did not influence the outlook greatly, since 36 per cent of this number died, as compared with a mortality of 32 per cent among all other patients. There was definite evidence that in 20 instances the fibrillation was transient. Two patients died soon after the first appearance of this arrhythmia, so that no opportunity was afforded to learn whether it would persist. Of the remaining 3 patients, 2 had auricular fibrillation both on admission to the hospital and on discharge after recovery, and it was impossible to tell when the irregularity first appeared. In only 1 case electrocardiograms taken before and after the acute attack yielded definite proof that persistent auricular fibrillation developed in conjunction with the myocardial infarction. Auricular fibrillation was slightly more common in patients with anterior infarction (15 out of 109) than in those with a posterior lesion (5 out of 63), but it carried a somewhat graver prognosis for the latter.

That paroxysmal ventricular tachycardia is not infrequently associated with acute coronary thrombosis was observed as early as 1921 by Robinson and Herrmann.^{8a} In this series there were 6 patients (3 per cent) in whom it was known to appear. All had infarction of the anterior part of the left ventricle, and one half of them succumbed. Paroxysmal auricular flutter occurred in 5 patients. One had a posterior infarct, and 4 had an anterior lesion. Three of them died. Premature beats of various types were common. In this series they occurred in 52

52. Master, A. M.; Dack, S., and Jaffe, H. L.: Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, *Ann. Int. Med.* **11**:735 (Nov.) 1937.

patients. The majority showed premature ventricular beats or premature auricular beats. Premature nodal beats and blocked premature auricular beats were less common. Extrasystoles did not alter the prognosis materially (33 per cent mortality). Auriculoventricular nodal rhythm was observed in 6 instances, and in 4 of these the patient did not recover. It is worth while to note here that in spite of the great variety of arrhythmias encountered in this series, we have found no instance of paroxysmal auricular tachycardia. Master and co-workers⁶² reported 3 cases in a group of 300 patients. It is our impression that this particular type of disturbed cardiac mechanism must be extremely rare in association with acute myocardial infarction.

In this paper we have grouped partial heart block and complete heart block together, for it was observed that patients showing one of these alterations commonly were found to show the other at some later time. There were 7 patients who fell into this particular group. It was striking that in none who survived after the first few days did the original degree of block persist. Two patients went through all three degrees of block and showed a normal mechanism on recovery. One showed 2:1 block, then a lesser degree of partial block, then simple delayed auriculoventricular conduction and finally a normal mechanism. Another patient showed, first, complete heart block and then delayed auriculoventricular conduction, which persisted. Still another showed this same change and then reverted to a 2:1 partial heart block, which persisted. It follows, therefore, that once heart block develops in association with acute myocardial infarction, if the patient survives, complete recovery from the block or a lesser degree of block tends to be the ultimate outcome. Among these patients, 5 had complete heart block at one time or another, and of these, 2 manifested Adams-Stokes attacks.

It is the general impression that partial or complete heart block is more commonly associated with posterior infarction than with an anterior lesion. The number of patients in this study was small but did show a trend in that direction, 4 having posterior infarction and 3 having a lesion located anteriorly. In order to learn if this relation would be borne out in a larger group we reviewed the cases of all patients seen at this hospital in the past ten years who had either partial or complete block in association with acute coronary thrombosis. The addition of these patients to those included in our present series made a total of 29. Of these the evidence pointed to posterior infarction in 20 and anterior infarction in 9. It was interesting to note that in this larger series, also, there was a definite tendency for the degree of block originally present to diminish, so that of the total of 19 patients who survived, 10 showed a normal cardiac mechanism at the time of discharge.

SUMMARY AND CONCLUSION

A study was made of the cases of 208 patients with acute coronary thrombosis observed consecutively at the Peter Bent Brigham Hospital. So far as could be judged clinically, only those patients were included whose attacks were regarded as initial. The findings present during the early hours or few days were those which were particularly analyzed, which course thereby eliminated the obvious terminal changes that so often predict fatality. The purpose of this investigation was to determine whether any of the findings during the early part of the illness can serve as a guide to prognosis. The significance of individual clinical and electrocardiographic features was therefore analyzed, with the following results:

Mortality.—The immediate mortality in the entire series was 33 per cent. Anterior infarctions occurred more commonly than posterior lesions, the proportion being 5:3, but the mortality was about the same with regard to the two locations. The mortality was distinctly higher for patients with bundle branch block and those with auriculoventricular block, but lower for those who showed low voltage of the QRS complex. A group that had electrocardiographic findings which were regarded as unclassifiable, i. e., without significant changes or abnormalities, also had a distinctly lower mortality.

Sex.—The proportion of men to women was 7:3. The prognosis for women was somewhat more grave.

Age.—The average age at the time of the attack was 58.7 years for the entire series—57.4 years for men and 61.5 years for women. The mortality progressively increased with advancing years. This held true regardless of the electrocardiographic findings.

Previous Angina Pectoris.—Antecedent angina pectoris was present in 72 per cent of all patients and was equal in its occurrence in the two sexes. Those patients with a previous history of such a condition had a lower mortality (29 per cent) than those without it (38 per cent).

Previous Hypertension.—Antecedent hypertension was present in 57 per cent of all patients, 44 per cent of the men, and 86 per cent of the women. It tended to increase the mortality in both sexes. Coronary occlusion in women who had neither previous angina pectoris nor hypertension was particularly rare.

Blood Pressure Changes.—The occurrence of a fall in systolic blood pressure of more than 20 mm. increased the mortality slightly, although a systolic level that was maintained below 80 mm. for many hours or days appeared to be serious.

Pain.—The severity or radiation of the pain had but little prognostic value, nor did it aid in the localization of the infarction. However, in

the small number of patients without pain in the chest there was a mortality decidedly higher than average. Anterior infarction with pain radiating to the left arm had a lower mortality (20 per cent) than similar infarction without this radiation (41 per cent). Radiation of pain to the right arm, as well as to the left, was slightly more common in association with posterior infarction. The occurrence of initial attacks of myocardial infarction without any pain or its equivalent symptoms was rare (3 per cent).

Dyspnea.—Dyspnea of some degree occurred in 71 per cent of patients. The mortality increased decidedly as dyspnea became more prominent, from 18 per cent for those with no dyspnea to 24, 36 and 62 per cent for those with mild, moderate and severe dyspnea, respectively. Dyspnea was much more helpful than pain in judging the prognosis.

Sweating.—Sweating occurred commonly but was of only slight prognostic significance. However, the presence of a moist skin days or weeks after the onset appeared to indicate that the dangerous period had not yet passed.

Cyanosis.—Cyanosis was found in about one-half the patients and indicated a distinctly higher mortality (45 per cent as compared with 16 per cent).

Shock.—Some degree of shock was present in 54 per cent of all patients. The mortality increased in direct proportion to the degree of shock: absent, 20 per cent; mild, 26 per cent; moderate, 51 per cent, and severe, 93 per cent.

Auscultatory Signs.—Gallop rhythm was noted in 20 per cent of all patients and was more common among those who died. It was more commonly associated with anterior than with posterior infarction, but was a more serious sign for patients with the latter lesion. The quality of the heart sounds was regarded as faint in over one-half the patients, and such sounds were more common in those who succumbed. The incidence of pericardial friction rub was 16 per cent. Although generally associated with anterior infarction, it was observed in 5 patients with a posterior lesion. Its appearance renders the outlook somewhat more grave (45 per cent, as compared with 31 per cent).

Temperature.—The rectal temperature was above 100 F. in 92 per cent of the patients. In 7 instances it was between 99 and 100 F. and in 3 it was below 99 F. There was a distinctly progressive rise in mortality with the increasing levels of fever.

Pulse.—When changes in the pulse rate due to such arrhythmias as paroxysmal rapid heart action and heart block were excluded, the heart rate in the great majority of patients was over 100 (average, 107). In

7 patients, however, the rate never rose above 80, and in 1 it was under 70. A slight tendency to increased mortality accompanied the more rapid rates.

Respiratory Rate.—The respiratory rate, in general, followed the pulse rate and the degree of dyspnea and was on the whole more rapid in the patients who died than in those who recovered.

Leukocyte Count.—A leukocyte count over 10,000 during the first week following the onset of the attack was found in 86 per cent of the patients. In 3 per cent the count was over 30,000. The mortality was 16 per cent for those with counts under 15,000 and 54 per cent for those with counts over that level.

Sedimentation Rate.—Although data concerning sedimentation rates were not numerous, the rates did not seem to be of much prognostic value.

Congestive Heart Failure.—About three fourths of the patients showed some objective evidence of congestive failure. The mortality steadily increased with increasing degrees of pulmonary congestion: absent, 10 per cent; slight, 30 per cent; moderate, 44 per cent, and marked, 68 per cent. A palpable liver was found in 29 per cent of the patients. This appears more frequent than one would expect in initial attacks of acute coronary thrombosis but probably reflects the greater gravity of conditions in patients coming to a public hospital. The presence of a palpable liver increased the mortality slightly. Peripheral pitting edema occurred in 22 per cent of the patients and was definitely associated with increase in the mortality (50 per cent with pitting as contrasted with 28 per cent without). Left heart failure occurred more commonly, but was slightly less serious with anterior than with posterior lesions. The combination of both right and left heart failure was equally common with anterior and with posterior infarction. It did seem that the presence of right heart failure was somewhat more serious in patients with an anterior lesion.

Complications.—Such complications as pulmonary infarction, pneumonia, psychosis, cerebral vascular accident and peripheral arterial embolus obviously made the outlook more serious. Among 37 patients examined post mortem, there were 3 with rupture of the ventricle and 15 with ventricular mural thrombosis. Six patients in this entire series had additional valvular disease. Sudden, unexpected death while patients were apparently doing well was found in some instances to occur without myocardial rupture.

Arrhythmias.—Some type of arrhythmia was observed in 38 per cent of these patients and tended to increase the mortality to a slight extent. Auricular fibrillation, almost always of the transient type, occurred in

12 per cent of the patients, paroxysmal ventricular tachycardia in 3 per cent (all with anterior infarction), paroxysmal auricular flutter in 2.5 per cent and extrasystoles of some form in 25 per cent. There was not a single instance of paroxysmal auricular tachycardia. Partial or complete heart block was present in 3.5 per cent of the patients and was more commonly associated with a posterior than with an anterior lesion. The degree of block tended to decrease or disappear if recovery occurred.

Electrocardiograms.—In a review of the electrocardiographic data in this study it appeared that the absence of any significant changes in the tracings indicated a distinctly more hopeful immediate outlook. When distinctly abnormal alterations in the ventricular complex were found, with few exceptions, it did not seem to matter greatly what they were, apart from important arrhythmias.

Conclusion.—It can be stated that the immediate outlook in a case of acute coronary thrombosis is extremely difficult to predict. Although many of the clinical and electrocardiographic features analyzed may indicate that the condition is either more or less critical, there is practically no criterion which is infallible. However, weighing all the information available together with the general appearance of the patient enables the physician to make a fair estimate as to the immediate prognosis.

IMPORTANCE OF THE DEXTROSE TOLERANCE TEST IN THE DIAGNOSIS OF MARGINAL MALNUTRITION

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The possibility of marginal malnutrition in so-called normal persons has been a subject of increasing interest in recent years. When malnutrition has reached the point where definite deficiency disease or marked wasting and dehydration have developed, the diagnosis is easy. In the prodromal states, however, no method has been presented whereby malnutrition can be determined except from the history or by the rather complex quantitative analysis for vitamins or other factors, i. e., procedures which are not very specific and which present technical difficulties to the practicing physician.

The diagnosis of developing malnutrition is an important one, especially in the case of the nervous type of patient, because malnutrition produces easy fatigability which, in turn, increases the severity of the subjective symptoms, such as nervous tension and irritability. An exact diagnostic procedure would be of great benefit not only in dealing with patients of the nervous type but in the general practice of medicine. We believe that the dextrose tolerance test, if properly interpreted, is such a procedure.

The high incidence of diabetic-like dextrose tolerance curves among patients of the nervous or mental type has been reported recently by Robinson and Shelton.¹ In order to try to determine the etiologic basis of these curves, which indicate disturbance in the ability to utilize and metabolize dextrose for energy, certain cases were selected from the original series for careful analysis to determine if they had a common etiologic denominator. We selected 5 cases which, according to three criteria proposed for the diagnosis of diabetes by tolerance curves, were instances of "diabetes mellitus," yet all the curves returned to "normal"

From Neurological Hospital.

1. Robinson, G. W., Jr., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves, *J. A. M. A.* **114**:2279 (June 8) 1940.

within a relatively short period. We also selected 2 cases with normal curves for comparison.

The three criteria by which the diagnosis of diabetes mellitus may be established by tolerance curves are those described by (1) Exton and Rose²; (2) Gould, Altshuler and Mellen,³ and (3) Matthews, Magath, Berkson and Gage.⁴

According to Exton and Rose, a diabetic tolerance curve is established when (1) a more or less steep rise of not less than 10 mg. of blood sugar following the second dose of dextrose is present and (2) "the relation of blood and urine sugar values to the severity of the disease" is given consideration.

The establishment of a diabetic tolerance curve by the criterion of Gould and co-workers is indicated when there are "(1) a fasting blood sugar which exceeds 120 mg. per hundred cubic centimeters; (2) a half-hour blood sugar which exceeds the fasting level by 50 mg. or more, and (3) a one hour blood sugar which exceeds the half-hour level by 30 mg. or more." When two of these three conditions are present, the diagnosis of diabetes mellitus can be made, according to the authors.

According to Matthews and co-workers:

If 158 mg. per hundred cubic centimeters of blood is taken as the critical level so that individuals showing a blood sugar reading below this level at the hour are designated nondiabetic and individuals with readings at or above this value are designated presumptively diabetic, a high percentage of correct diagnoses can be expected. As far as the observations in this series are concerned, all individuals with values at the hour less than 154 mg. were found to be normal, and all individuals with values at the hour of 180 mg. or more were found to be diabetic.

Two of us presented in a previous paper¹ case analyses which showed that according to Exton and Rose 60.8 per cent, according to Gould and co-workers 36.3 per cent and according to Matthews and associates 54.5 per cent of our consecutively admitted patients could be given the diagnosis of diabetes or presumptive diabetes.

In selecting 5 of the cases for this study, we adhered strictly to these criteria and took only those cases in which the patient's condition could be diagnosed as diabetes mellitus by all three standards. These cases

2. Exton, W. G., and Rose, A. R.: Diabetes as a Life Insurance Selection Problem, *Proc. A. Life Insur. M. Dir. America* (1931) **18**:252, 1932; The One-Hour Two-Dose Dextrose Tolerance Test, *Am. J. Clin. Path.* **4**:381, 1934.

3. Gould, S. E.; Altshuler, S. S., and Mellen, H. S.: The One-Hour Two-Dose Glucose Tolerance Test in the Diagnosis of Diabetes Mellitus, *Am. J. M. Sc.* **193**:611 (May) 1937.

4. Matthews, M. W.; Magath, T. B.; Berkson, J., and Gage, R. P.: The One-Hour Two-Dose Dextrose Tolerance Test (Exton-Rose Procedure), *J. A. M. A.* **113**:1531 (Oct. 21) 1939.

were selected to show that, although the patients had definite diabetic curves, the curves probably indicated malnutrition. With proper treatment, these curves returned to normal, and since discharge these patients have maintained normal carbohydrate metabolism without treatment. We shall endeavor to show by analysis of cases a common etiologic denominator, namely, malnutrition.

Cases of mental conditions of various types make up our material. Patients with such conditions are excellent material for studies in malnutrition, especially of the marginal type, because their habits and symptoms lead to this state and these physiologic abnormalities will

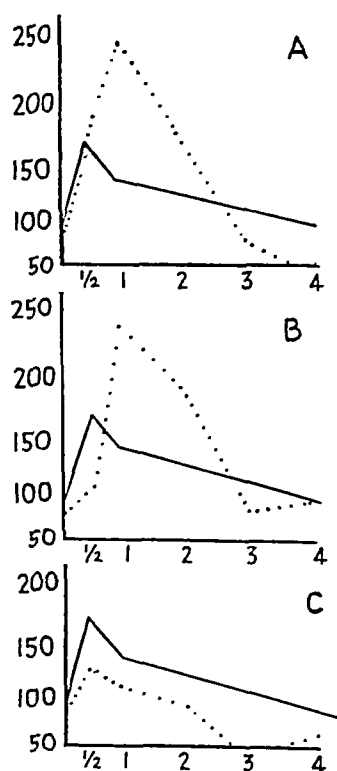


Fig. 1.—Dextrose tolerance curves for F. P. (case 1) obtained (A) Sept. 2, 1939, the day following admission to the hospital, (B) October 18, forty-six days after the first test, and (C) November 13, seventy-two days after the first test.

develop in any person who suffers from malnutrition. These interpretations are in the field of internal medicine. The underlying psychiatric factors are, we believe, incidental in this presentation.

CASE 1.—F. P., a white woman aged 32, was admitted to the hospital Aug. 30, 1939 with the chief complaint of negativism. The onset of her condition, which followed severe financial worry and strain, coupled with the birth of 2 children, began approximately three years before. Until two weeks before admission to the hospital she was in a state of profound agitation and depression, which had progressed since its onset some three years before to an acute condition. During this interval the patient lost 15 pounds (6.8 Kg.). That her metabolic processes were seriously impaired was indicated by the fact that for several weeks after entrance to the hospital she continued to lose weight, despite the fact

that she received insulin and intravenous injections of dextrose and ate 100 per cent of her regular diet. Previous to admission the patient never reached the state in which she refused food, but it was apparent from the loss in weight that she received little energy value from her food. At the time of examination she was hyperactive and agitated, and her activity continued for two weeks. Physical examination revealed nothing which suggested a pathologic cellular condition. The red cell, the white cell and differential counts of the blood were normal, and chemical studies on September 1 revealed that the nonprotein nitrogen was within the normal range and the fasting blood sugar was 72.7 mg. per hundred cubic centimeters. There were traces of sugar and albumin in the urine. The patient's dextrose tolerance curve is illustrated in figure 1 *A*. The fasting blood sugar, as shown, was 82.0 mg. per hundred cubic centimeters on September 2. At the one-half hour interval the blood sugar had risen to 175.4 mg. and at the one hour mark to 250.0 mg.; by the fourth hour it had fallen to 48.4 mg. The urine gave a 2 plus reaction for sugar both at the end of the first hour and at the end of the test. This curve, by all three criteria outlined, is characteristic

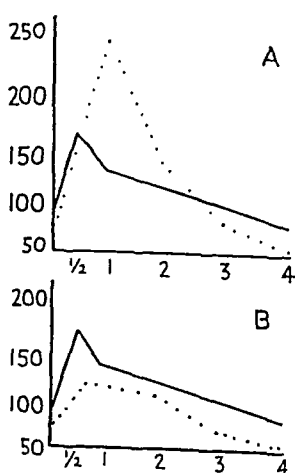


Fig. 2.—Dextrose tolerance curves for M. P. (case 2) obtained (*A*) Sept. 3, 1939, the day following admission to the hospital, and (*B*) November 8, thirty-five days later, during which period insulin and metrazol shock therapy was given.

of diabetes. The test was repeated on October 18 and on November 13. On the former date the curve was much the same as on September 2, but on the latter date it was normal; it has remained so since her dismissal from the hospital.

On September 4 the patient began receiving metrazol and insulin shock therapy. In all she had twelve metrazol shock reactions. She began to improve two weeks after entrance into the hospital and was discharged October 25. Her condition since discharge has been excellent; she is enjoying the best of health and has had a complete psychiatric remission.

CASE 2.—M. P., a white woman aged 34, was admitted to the hospital Sept. 2, 1939, with the chief complaint of fear and anticipation of future events. In 1931 she had had an appendectomy, and later Malta fever developed. After that she became cachectic and was given small doses of insulin to stimulate appetite. She began to lose weight; her condition became progressively worse, and on her admission to the hospital she weighed 81½ pounds (37 Kg.). Examination at the time of admission revealed a person of slight build who had apparently lost considerable weight and manifested few signs of activity. No other gross abnor-

malities were apparent. There was a trace of sugar in the urine. The white blood cell count was 11,875, with a normal red cell count. Chemical studies of the blood gave a sugar value of 65.6 mg. per hundred cubic centimeters and a nonprotein nitrogen value within normal limits. The cholesterol content of the blood was 226 mg. per hundred cubic centimeters. The dextrose tolerance curve, as shown in figure 2 *A*, was a typical diabetic curve, according to the criteria. From a fasting level of 65.6 mg. per hundred cubic centimeters the blood sugar rose to 250.0 mg. at the one hour interval, and by the fourth hour it had dropped to 55.6 mg. A trace of sugar was found in the urine at the end of one-half hour, and the reaction was 3 plus and 4 plus at the one and two hour periods, respectively. No sugar was present in the four hour sample. This test was run the day after admission, and the resultant curve conforms to all three criteria of a diabetic curve. The patient's condition was diagnosed as schizophrenia, and she was given insulin and metrazol shock therapy. Approximately four weeks was required to improve her physical condition to the point where she could undertake these treatments with safety. On November 8, before her discharge

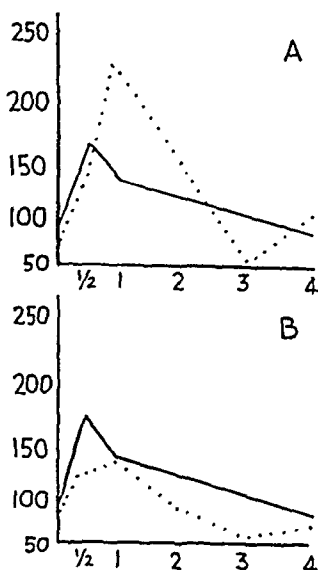


Fig. 3.—Dextrose tolerance curves for J. C. (case 3) obtained (*A*) Sept. 5, 1939, the second day following admission to the hospital, and (*B*) October 16, forty-one days later, during which period metrazol shock therapy was given.

from the hospital, another dextrose tolerance test was run. We found the curve to be normal. Her fasting blood sugar level was 69.0 mg. per hundred cubic centimeters. The next sample showed the peak at 133.3 mg., and by the fourth hour the blood sugar level was 59.8 mg. At no time was any sugar detected in the urine. By the time of discharge from the hospital the patient had gained $12\frac{3}{4}$ pounds (5.7 Kg.). She has continued in good physical condition, although to a certain extent there has been a recurrence of her mental condition.

CASE 3.—J. C., a white man aged 56, was admitted to the hospital Sept. 3, 1939, with the chief complaints of depression, melancholia, anorexia and apprehension. His condition had come on gradually, dating back to April 1939, at which time he began to complain of gastrointestinal disturbances, loss of appetite, etc. The symptoms that he showed on admission had developed the preceding June. For a month prior to his admission he had eaten no solid food and had shown profound depression. Examination showed him to be well developed but emaciated. Other physical findings and the medical history were essentially of

no significance. The urine was normal, the nonprotein nitrogen was within normal limits and the fasting blood sugar was 75.3 per hundred cubic centimeters. A blood count, including a differential count, was within normal limits. The second day following admission a dextrose tolerance test was run. The resultant curve showed a fasting blood sugar of 73.3 mg. per hundred cubic centimeters. The blood sugar rose and reached its peak at the end of the first hour, at which time the reading was 235.3 mg. At the end of the second and the third hour it dropped to 161.3 and 51.7 mg., respectively. At the fourth hour it rose again to 129.0 mg. The patient's condition was diagnosed as an agitative depressive psychosis, and metrazol shock therapy was given. Intravenous injections of a 10 per cent solution of dextrose and vitamin B₁ (thiamine hydrochloride) also were given in the course of the treatment. The patient's psychosis cleared, and he was discharged from the hospital November 21, with a complete remission. Shortly prior to his discharge another dextrose tolerance test was run. The

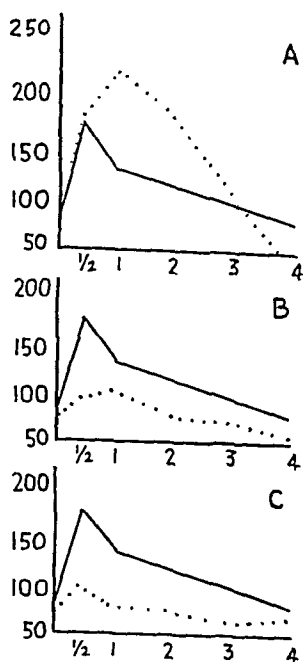


Fig. 4.—Dextrose tolerance curves for W. B. (case 4) obtained (A) Sept. 1, 1939, three days after admission to the hospital, (B) September 9, after eight days of treatment for alcoholism, and (C) September 19, after nineteen days of treatment for alcoholism.

fasting blood sugar was found to be 84.7 mg. per hundred cubic centimeters. At the end of one hour the level was 140.8 mg. It then dropped in the second and the third hour to 97.6 and 57.5 mg., respectively. At no time during this test was any sugar found in the urine.

CASE 4.—W. B., a white man aged 37, was admitted to the hospital Aug. 29, 1939, in a state of profound physical exhaustion. The chief complaint was alcoholism. The onset of his condition had occurred insidiously several years earlier. He had eaten very little for some weeks prior to his admission. The dextrose tolerance test, along with other laboratory studies, was done on admission, and with the exception of the tolerance curve, all results were essentially irrelevant. The fasting level of the blood sugar, as indicated in figure 4 A, was 114.0 mg. per hundred cubic centimeters. At the end of one-half hour it had risen to 163.9

mg., and the one hour sample showed the peak of 227.3 mg. At the end of two hours the blood sugar level had dropped to 190.5 mg. and one hour later to 129.8 mg. The four hour sample showed the blood sugar to be 40.0 mg. Sugar in the urine reached its peak, a 3 plus reaction, at the first hourly interval, coincident with the high blood sugar level. This curve, according to all three criteria, is diabetic. This patient was treated for alcoholism, and in eight days another test was run. This time the curve was more nearly normal, with the following data: fasting level, 80.0 mg.; one-half hour, 103.1 mg.; two hours, 93 mg.; three hours, 81.6 mg., and four hours, 51.5 mg. The urine gave a negative reaction for sugar throughout the test. On September 19 another dextrose tolerance test was run, with the following results: fasting level, 80.0 mg.; one-half hour, 110.5 mg.; one hour, 88.9 mg.; two hours, 85.1 mg.; three hours, 69.1 mg., and four hours, 74.1 mg. The urine again gave a negative reaction for sugar. This curve, although low, is normal for this man. It is evident that he is not diabetic, but he could have been classified as such on admission by all three criteria. This patient, like those in cases 1, 2 and 3, showed this curve, we believe, because of pronounced malnutrition, in this case due to metabolic disturbances accompanying alcoholism.

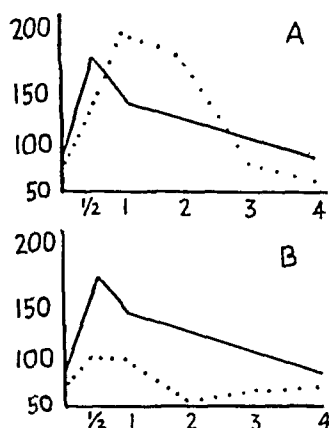


Fig. 5.—Dextrose tolerance curves for H. K. (case 5) obtained (A) Nov. 5, 1939, the day following admission to the hospital, and (B) November 19, after fourteen days of treatment for alcoholism.

CASE 5.—H. K., a white man aged 44, was admitted to the hospital on Nov. 4, 1939, with the chief complaint of alcoholic toxemia. He was in a state of acute alcoholism on admission and was weak and malnourished. Physical examination revealed nothing else of importance. Laboratory examination of the blood and urine revealed nothing outstandingly abnormal except the dextrose tolerance. A tolerance test was run November 5, and the following results were obtained: fasting blood sugar, 70.4 mg.; one-half hour, 147.0 mg.; one hour, 200.0 mg.; two hours, 186.9 mg.; three hours, 80.0 mg., and four hours, 60.2 mg. Sugar in the urine at the beginning of the test was 0.5 mg. per hundred cubic centimeters. By the end of the second hour it was 5.75 mg., and it dropped by the third hour to 0.75 mg. Only a trace was found at the end of the fourth hour. The dextrose tolerance test was repeated November 18, with the following results: fasting blood sugar, 78.1 mg.; one-half hour, 109.9 mg.; one hour, 108.1 mg.; two hours, 45.5 mg.; three hours, 60.0 mg., and four hours, 66.7 mg. This curve is within normal limits; no sugar was found in the urine at any time.

In these 5 cases the only common denominator is malnutrition. In order to illustrate this point further, the cases of 2 patients with similar

chief complaints but with normal dextrose tolerance curves were selected for analysis.

CASE 6.—G. G., a white woman aged 39, was admitted to the hospital Oct. 10, 1939, with the chief complaint of alcoholism. The onset of her condition occurred about three years earlier, after a motor car accident in which a person was killed. At that time she began to drink excessively and continuously. On physical examination at the time of admission she appeared well nourished, although acutely intoxicated. Results of laboratory studies, including the dextrose tolerance test, were essentially normal. The following results were obtained from the tolerance test: fasting blood sugar, 71.9 mg.; one-half hour, 140.8 mg.; one hour, 72.6 mg.; two hours, 66.4 mg.; three hours, 89.3 mg., and four hours, 88.9 mg.

We present this case for comparison with cases 4 and 5, in both of which alcoholism was the chief complaint. We wish to stress that in cases 4 and 5 the tolerance curve was diabetic but in case 6 there was no disturbance of the tolerance curve, despite the patient's condition of chronic alcoholism. In all 3 of these cases the patients were, and had

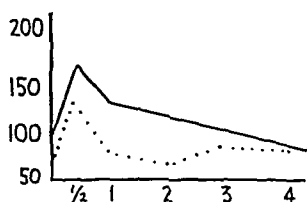


Figure 6

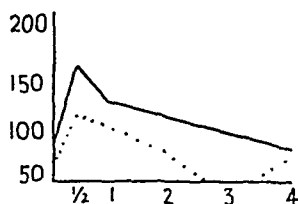


Figure 7

Fig. 6.—Dextrose tolerance curve for G. G. (case 6) obtained Oct. 11, 1939, the day following admission to the hospital.

Fig. 7.—Dextrose tolerance curve for G. Gen. (case 7).

been for some time, acutely intoxicated. All presented similar histories with only one variable—nutrition. The patient in case 6 had by proper diet kept her metabolic processes normal throughout her drinking episodes, while the other 2 had not and hence were suffering from malnutrition.

CASE 7.—G. Gen., a white man aged 54, was admitted to the hospital Sept. 18, 1939, in a state of hypomania, the onset of which occurred only a short time prior to admission. After a period of most severe physical and emotional stress, a typical manic psychosis had developed. Physical examination revealed a state of average nutrition but no pathologic condition or gross physical defects. Results of laboratory tests were essentially without significance, and the following tolerance curve, which is nondiabetic in character, was obtained: fasting blood sugar, 75.5 mg.; one-half hour, 129.0 mg.; one hour, 121.2 mg.; two hours, 93.0 mg.; three hours, 44.1 mg., and four hours, 66.6 mg.

The results in this case, and in several similar ones in our files, show that there is apparently no constant relation between manic-depressive episodes and a high dextrose tolerance curve. Diethelm,⁵ Wittkower,⁶

5. Diethelm, O.: The Influence of Emotions on Dextrose Tolerance, *Arch. Neurol. & Psychiat.* 32:342 (Aug.) 1936.

McGowan⁷ and Tod⁸ have reported on disturbed dextrose tolerance curves associated with certain abnormal emotional states and with various psychotic reactions. They concluded that the disturbance of the dextrose tolerance curve was the result of the mental condition affecting bodily functions and reactions, that it had no etiologic significance and that it indicated an abnormal utilization of dextrose. Our observations do not seem to confirm their conclusions. Some of our most disturbed patients have a normal tolerance for dextrose, while many of our apparently calm patients, who give a history of malnutrition, have a poor tolerance, i. e., a diabetic-like curve.

COMMENT

We have analyzed these 7 cases to show that a diagnosis of clinical malnutrition can be confirmed with the help of the dextrose tolerance test. Frank disorders of metabolism and nutrition are, of course, obvious, but cases of marginal or developing malnutrition present no outstanding objective clinical signs, and it seems to us that the test in this respect should be valuable to the physician in general practice.

In our first 5 cases there was no question as to the presence of malnutrition, and in the last 2 there was no evidence of any kind in the history or examination of malnutrition or metabolic change. Between these two extremes there are, in our 200 cases, conditions representing all the stages of developing malnutrition, up to and including pellagra and beriberi. The two extreme conditions should be easy to interpret and diagnose. However, both in psychiatric and in general practice there are many cases in which there is a history of easy fatigue and other symptoms of malnutrition that make determination of the state of nutrition an important factor. It is in these cases that we have found this test and its interpretation of greatest importance. When we first began to determine tolerance curves routinely, we were greatly surprised at the findings, for it soon became evident that the most disturbed tolerance curves occurred in the cases of the most profound malnutrition. We could find no other common denominator. This interpretation was confirmed by the return of these curves to normal after therapy was directed at the malnutrition. The state of the psychosis had no effect on the curves. In some cases psychiatric recovery ensued without a return of normal metabolism; in others the curves returned to normal while the psychosis was still as active as at the time of admission.

6. Wittkower, E.: The Influence of Emotions on Somatic Functions, *J. Ment. Sc.* **81**:533 (July) 1935.

7. McGowan, P. K.: Manic-Depressive Psychosis-Symposium: Hyperglycemic Index as Aid in Prognosis, *J. Ment. Sc.* **82**:589 (Sept.) 1936.

8. Tod, H.: Studies in Carbohydrate Metabolism in Mental Disorders, *Edinburgh M. J.* **43**:524 (Aug.) 1936.

When we analyzed the cases in the intermediate group, in which the history of malnutrition was indefinite or absent, we found that some of the curves were normal, while others were diabetic. The response of the curves to therapy was the same as in the cases of profound malnutrition. The only possible conclusion in the absence of some additional factor or evidence not yet apparent is that in those cases in which an indeterminate history was associated with a disturbed curve malnutrition was present. In some cases careful questioning brought out the story of an inadequate or improper diet, although the patient or his family had thought the diet suitable.

We consider that the dextrose tolerance test is a satisfactory test for the state of nutrition, as well as for diabetes mellitus, and believe that in cases in which the situation might indicate malnutrition, a dextrose tolerance test should be done and interpretations made from the standpoint of possible nutritional deficit, as well as from the standpoint of diabetes.

In 5 cases in which there were a typical history of malnutrition and physical evidence of long-standing improper metabolism we have shown that the dextrose tolerance curve was diabetic and that a diagnosis of diabetes mellitus could have been made at the time of admission. We have also shown that when proper nutrition was reestablished the tolerance curve returned to normal and remained so, without subsequent treatment of any kind other than a full diet. We have also presented 2 cases, of the same clinical type as some in which there were abnormal curves, in which a history of a full diet and absence of any metabolic change up to the time of admission were associated with normal curves.

These are selected cases, chosen because of the specificity of the findings. Our total group of cases in which tolerance tests were made has now reached approximately 200, as compared with that of 69 originally reported, and we find that this common denominator (malnutrition) runs throughout. In all cases in which the curves were not truly or frankly diabetic, the curve returned to normal within one to three months of the time that adequate nutrition was started.

Bowman, Wortis, Orenstein and Goldfarb⁹ made a study of dextrose tolerance in a group of 18 patients with alcoholism. They reported:

On admission there was a marked diminution of the sugar tolerance, which improved after one week in the hospital on a normal diet. It is suggested that the diminished tolerance was due to an undernourished state previous to admission.

Chambers¹⁰ outlined the physiologic generalizations behind the concept of clinical marginal malnutrition as it affects the factors controlling

9. Bowman, K. M.; Wortis, J.; Orenstein, L., and Goldfarb, W.: The Sugar Tolerance of Alcoholic Patients, *Proc. Soc. Exper. Biol. & Med.* **42**:37 (Oct.) 1939.

10. Chambers, W. H.: Undernutrition and Carbohydrate Metabolism, *Physiol. Rev.* **18**:248 (April) 1938.

carbohydrate metabolism and the dextrose tolerance of the patient. We quote the opening paragraphs of his recent review.

Undernutrition is used in a broad sense in this paper to include complete inanition as well as the dietary deficiencies. Fasting has been recognized as a factor in carbohydrate metabolism since 1873, but the greatest expansion of the entire field has occurred in the past 15 years. During this time the endocrine control of carbohydrate metabolism has been developed and now occupies a position of major importance. An attempt to correlate the studies of undernutrition and the endocrine research has led to the following generalizations concerning carbohydrate utilization.

The maximum utilization of administered glucose is found in the normal individual when carbohydrate has been abundantly supplied in the diet. The minimum effect is obtained in the completely depancreatized animal which excretes all of the ingested sugar in the urine. Between these extremes is a series of less sharply defined intermediate stages. As the amount of carbohydrate in the diet is diminished the glucose tolerance test indicates a decreased utilization. During complete inanition there is a progressive deprivation of the carbohydrate stores in the body and an increasingly larger fraction of the test meal is lost by excretion as the fast continues. A more drastic and exaggerated condition is seen in the animal depleted by phlorhizin glycosuria. Approaching pancreatic diabetes at the lower end of the scale are the various stages of diabetes mellitus and the endocrine disturbances involving the pituitary and the adrenal. Of the many factors exerting a controlling influence on the different degrees of carbohydrate utilization as outlined, the importance of two is apparent—the amount of carbohydrate available to the cells and the endocrine control. The former seems to predominate at the beginning of the series but is superseded by the latter toward the minimum end. The literature presented in this review will give the evidence supporting these generalizations, with particular emphasis on the nutritional condition with respect to carbohydrate.

The conception of carbohydrate metabolism outlined above is based on the measurement of the body's ability to utilize carbohydrate, as determined by its reactions for several hours after the administration of pure glucose. When a glucose test meal is ingested sufficient in amount to maintain the maximum rate of absorption from the intestines for several hours, the total heat production of the body indicates that in the normal well-fed organism only about one-quarter to one-third of the absorbed sugar can be oxidized to CO_2 and H_2O . The major portion of the remainder is probably stored as glycogen, but conversion into fat, glycolysis to lactic acid, transformation into hexosephosphate, glycerophosphate, glucosamine, or other compounds may occur. These reactions may be observed in several ways. The method most extensively used for the study of carbohydrate metabolism has been the glucose tolerance test in which the rise and fall in blood sugar concentration are determined for several hours after the administration of sugar. This test is most useful in showing small differences in utilization. It should be remembered that the blood sugar changes reflect the rate but not the nature of glucose utilization. If the impairment is large enough, information as to the total amount utilized may be obtained from the quantitative collection of the fraction excreted by the kidney. The most direct evidence for oxidation comes from carefully conducted determinations of the respiratory metabolism sufficient in duration to yield combustion quotients when interfering changes in the body are adequately controlled (Richardson, 1929). Tissue analyses yield data concerning glycogen deposition and other methods of disposal. All of these reactions must be considered in establishing a complete picture of carbohydrate

utilization. The terms "utilization" and "oxidation" have been used synonymously in some of the recent literature. This is obviously inexact in short experiments.

We believe that a diagnosis of diabetes mellitus should not be made until the possibility of malnutrition has been eliminated by maintaining over a rather long period a full diet, supplemented by vitamins of the B complex and insulin in small doses (5 to 10 units), in order to revitalize the mechanisms of carbohydrate metabolism. If the curve returns to normal and remains normal for one month while the patient is taking a full diet but no insulin, then the diagnosis of malnutrition has been confirmed. If, however, the curve does not return to normal during a three month trial period or becomes abnormal again when the insulin is stopped but a full diet maintained, then a diagnosis of diabetes must be considered as the probable interpretation of the tolerance disturbance.

Millions of dollars are being spent annually on vitamins. We feel that much of this is wasted because administration of vitamins as a deficiency therapy is indicated only when malnutrition is present. If there is no malnutrition, synthetic or extracted vitamins are not needed. The members of the vitamin B complex are given indiscriminately in cases of alcoholism, nervous disturbance, mild psychosis, etc.; yet in many cases of such conditions there is no malnutrition and, therefore, no need for vitamin therapy.

We believe that whenever the presence of malnutrition is suspected, a dextrose tolerance test should be done. The results will usually confirm or deny the diagnosis. When an abnormal tolerance curve is present, malnutrition should be diagnosed and treated; when such a curve is not present, nutritional therapy is not indicated. As a result of these studies we wish to reaffirm our previous statement that the diagnosis of diabetes should be approached with caution when the diagnosis of malnutrition is a possible alternative.

CONCLUSIONS

1. Malnutrition disturbs the dextrose tolerance of the patient and produces a clinical condition which might be called pseudodiabetes.

2. Early developing or marginal malnutrition should be considered as a possible diagnosis whenever the dextrose tolerance curve is diabetic-like.

3. The nervous or psychotic patient should be relieved of his malnutrition by appropriate means before intensive therapy of other types is started, but it is not necessary to wait for the tolerance curve to return to normal before the other measures are instituted.

4. A diagnosis of diabetes mellitus should not be made until an appropriate period of treatment with a full diet has passed without the return of the dextrose tolerance curve to normal.

ACUTE, MASSIVE HEMOGLOBINURIA OF OBSCURE CAUSE, WITH JAUNDICE AND ANEMIA

REPORT OF A CASE WITH CLINICAL AND HEMATOLOGIC STUDIES
AND MEASUREMENTS OF THE BLOOD
PIGMENT METABOLISM

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AND

D. ROURKE GILLIGAN, M.S.

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Hemoglobinuria is encountered in several well defined clinical conditions in which intravascular hemolysis occurs. In the present study an unusual case of acute, severe hemoglobinuria, accompanied by jaundice and slowly developing anemia, with final recovery, is reported.

The clinical and laboratory findings in this case do not conform completely with those in any recognized type of hemolytic attack leading to hemoglobinuria. The diagnostic procedures utilized are discussed. The effects of posture and of exercise on the production of hemolysis were investigated.

The continuation of the hemolytic attack for three weeks in this case gave an unusual opportunity for studying the quantitative aspects of the hemolysis. Hematologic studies were made; the plasma and the urine hemoglobin and the plasma bilirubin were studied quantitatively, and the urinary and fecal excretions of urobilinogen were measured. The total amount and rate of hemolysis during the attack have been calculated from certain of these data.

METHODS OF INVESTIGATION

The hematologic and chemical methods employed have been outlined in some detail in previous articles.¹ Briefly, they were as follows: The method of Evelyn²

From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. (a) Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, *J. Clin. Investigation* **20**:177, 1941. (b) Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of the Clinical Characteristics and Mechanism, with Observations in Three New Cases, and Review of the Literature, *Medicine* **20**:34, 1941.

2. Evelyn, K. A.: A Stabilized Photoelectric Colorimeter with Light Filters, *J. Biol. Chem.* **115**:63, 1936.

was used in measuring blood hemoglobin; reticulocytes and platelets were counted in wet preparations according to Dameshek;³ hematocrit values were measured on samples of blood, with oxalate mixture as anticoagulant,⁴ in Rourke-Ernstene sedimentation tubes;⁵ the resistance of the red blood cells to hypotonic solutions of sodium chloride was measured according to Daland and Worthley;⁶ the lysolecithin fragility test was made by the method of Singer;⁷ plasma bilirubin was measured by the method of Malloy and Evelyn⁸ (as described previously,^{1a} the bilirubin values obtained by this method are appreciably lower than the actual values when the plasma contains hemoglobin in concentrations over 30 mg. per hundred cubic centimeters); the plasma and urine hemoglobin values were measured as described by Bing and Baker,⁹ with modifications outlined in a previous article;^{1a} the total protein of the urine was measured gravimetrically after precipitation with trichloroacetic acid;^{1a} the urea clearance was measured according to Van Slyke, Page, Hiller and Kirk;¹⁰ urobilinogen in the urine and the stool was measured according to Watson;¹¹ the Donath-Landsteiner test was conducted according to Mackenzie¹² (guinea pig complement was added), and the acid hemolysis test for diagnosis of the paroxysmal nocturnal type of hemoglobinuria was made according to Ham.¹³ Hemoglobin pigments in the blood and urine were identified by spectroscopic and spectrophotometric examination. The same precautions were exercised here as in previous work to prevent extravascular hemolysis during

3. Dameshek, W.: A Method for the Simultaneous Enumeration of the Blood Platelets and Reticulocytes, with Consideration of the Normal Blood Platelet Count in Men and in Women, *Arch. Int. Med.* **50**:579 (Oct.) 1932.

4. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, *J. Lab. & Clin. Med.* **19**:777, 1934.

5. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, *J. Clin. Investigation* **8**:545, 1930.

6. Daland, G. A., and Worthley, K.: The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride: Observations in Blood Disorders, *J. Lab. & Clin. Med.* **20**:1122, 1935.

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11. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am. J. Clin. Path.* **6**:458, 1936.

12. Mackenzie, G. M.: Paroxysmal Hemoglobinuria, *Medicine* **8**:159, 1929.

13. Ham, T. H.: Studies on Destruction of Red Blood Cells: I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, *Arch. Int. Med.* **64**:1271 (Dec.) 1939.

the drawing and handling of the samples of blood.¹⁴ The blood volume was calculated from data given by Gibson and Evans,¹⁴ which correlate the blood volume of normal persons with the surface area.

REPORT OF CASE

J. Y., a 77 year old Russian-Jewish retired barber, was admitted to the genito-urinary service of the Beth Israel Hospital on April 21, 1940 because he had passed several specimens of "black" urine during the previous twenty-four hours. The family history was irrelevant. The patient had had typhus fever, characterized by high temperature, severe headache and "spots all over the body," when in Europe during the Russo-Turkish War, in 1877. After this he was entirely well until 1930, when a right inguinal hernia developed, which was operated on at this hospital a year later. In 1936 a strangulated right femoral hernia and in 1939 an incarcerated left femoral hernia were operated on. In 1937 he received treatment in the outpatient department for hypertrophic arthritis, which had begun to cause symptoms a year earlier. On several examinations, in the period between 1931 and 1939, he was found to have a blood pressure of approximately 160 systolic and 90 diastolic, cardiac enlargement with an apical systolic murmur, pulmonary emphysema, a few rales over the base of the left lung, peripheral arteriosclerosis, varicose veins in the legs and an epigastric hernia. There was no enlargement of the liver or the spleen. Occasionally he experienced slight burning on urination. Several examinations between 1931 and 1937 revealed a red blood cell count of approximately 4,900,000 per cubic millimeter; normal urine, with specific gravity as high as 1.025; normal blood nonprotein nitrogen values and negative reactions to the Wassermann, Hinton and Kahn tests. In 1939 his urine contained small amounts of albumin and occasional leukocytes and erythrocytes and had a specific gravity of 1.020. Shortly thereafter, about four months before his present admission, he noted nocturia, with micturition twice a night. Beginning in 1936, he showed gradual loss in weight, amounting to 30 pounds (13.6 Kg.) in four years. He had taken no medication at any time during his life, except during his various periods of hospitalization, and had never been exposed to noxious chemicals.

On April 20, after sitting in a cinema for three hours, the patient voided "black" urine. During the night he voided eight or nine times, passing "black" urine each time and experiencing slight burning on urination. Between 7 a. m. and 12 noon of the next day he experienced considerable urgency but was unable to void. He was admitted to the hospital at noon and passed 14 ounces (414 cc.) of dark burgundy red urine shortly after admission; there were no further indications of suppression of the urinary flow. Physical examination gave information as previously noted, with the addition of slight icterus, enlargement of the liver to 4 cm. below the costal margin and a barely palpable spleen. The body temperature was 99.5 F. (rectal).

14. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, *J. Clin. Investigation* **16**:317, 1937.

Examination of the urinary sediment revealed only rare red blood cells and a few white blood cells. After centrifugation the urine gave strongly positive reactions to the guaiac and benzidine tests. The specific gravity was 1.007 and the reaction slightly alkaline. The nitric acid test showed a large amount of "albumin." The plasma was dark red and gave a strongly positive benzidine reaction.

Hematologic examination on the following morning (April 22) showed a red blood cell count of 4,710,000 per cubic millimeter, a hemoglobin concentration of .94 per cent (Evelyn) and a white blood cell count of 10,000 per cubic millimeter, with 67 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes and 10 per cent monocytes. The fragility of the red blood cells to hypotonic solutions of sodium chloride was normal. At this time the blood nonprotein nitrogen was 90 mg. per hundred cubic centimeters, and on the following day it was 78 mg. per hundred cubic centimeters, with a value for blood urea nitrogen of 44 mg. per hundred cubic centimeters. The urea clearance was 20 per cent of normal.

The clinical diagnosis on admission was hemoglobinemia, hemoglobinuria, icterus, hypertension, generalized arteriosclerosis, hypertensive heart disease, cardiac enlargement, chronic nephritis, pulmonary emphysema, varicose veins and epigastric hernia.

The patient was given a house diet and 3,600 cc. of fluids daily. Five grams of sodium bicarbonate was administered orally six times daily; this medication was reduced to 4 Gm. daily on April 25 and was discontinued on May 2. The urine was burgundy red for the first three days after admission, and hemoglobin did not completely disappear from the urine until about three weeks later (figure). The icterus increased during the first four days after admission, became moderately intense and disappeared during the next week. Because of the development of moderate anemia, administration of exsiccated ferrous sulfate, 0.2 Gm. four times daily, was started on May 8 and continued until July 10. Nocturia, with micturition three or four times a night, persisted throughout the patient's stay in the hospital. The stools were all of normal color. On the third and fourth days of the attack the stool showed a 4 plus guaiac reaction; several subsequent examinations of stools at intervals during the following months showed negative guaiac reactions.

The patient vomited on the day of admission. During the first three days of his stay in the hospital he experienced mild anorexia and heartburn and some constipation, cramps and distention, relieved by enemas; these disturbances did not recur. There was slight burning on urination at various times. The patient otherwise felt well, except for weakness and mild dyspnea on exertion a week after admission, when he was first allowed out of bed. The body temperature was not elevated at any time.

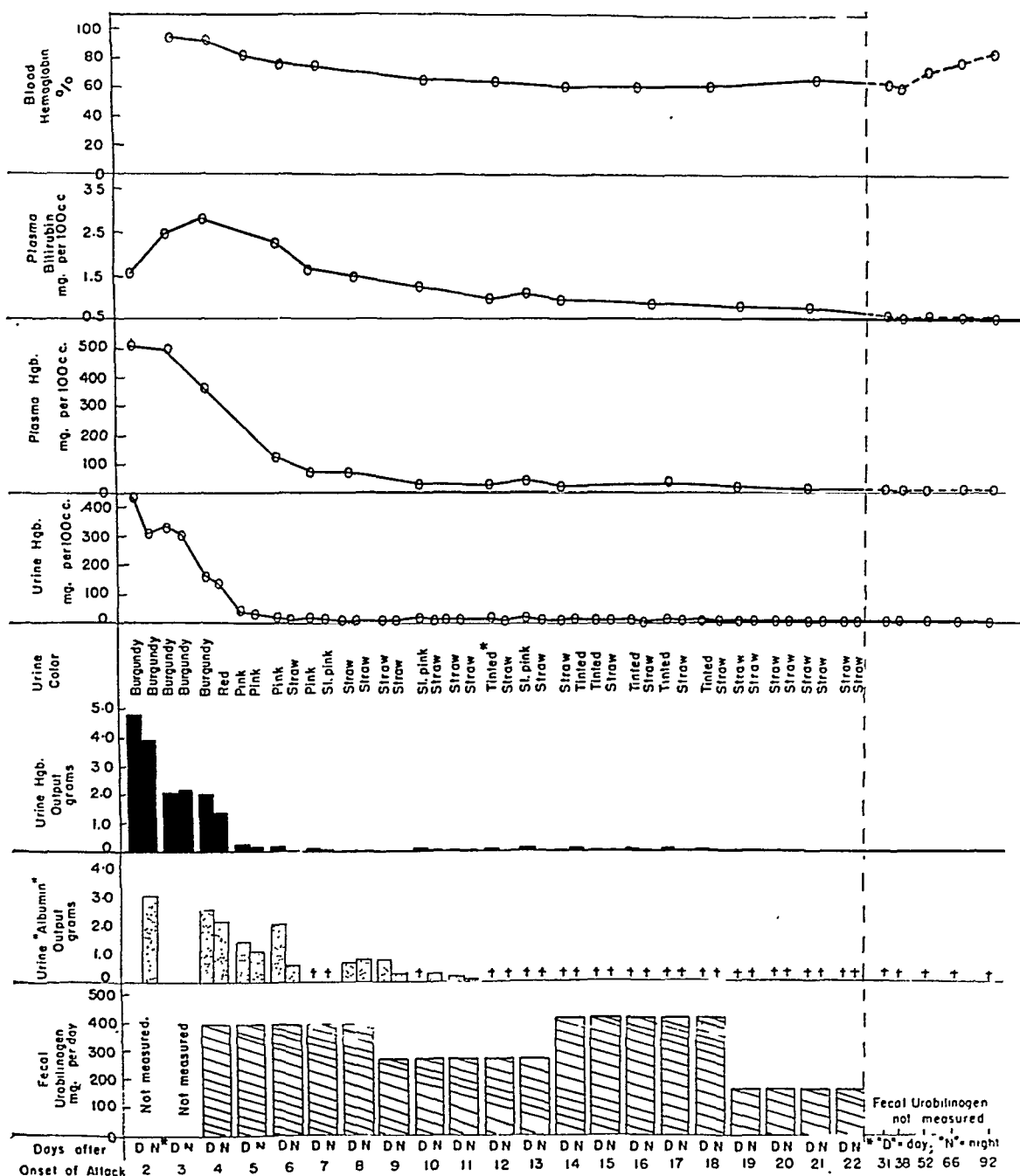
Roentgenographic studies on April 23 revealed the following conditions: hypertrophic arthritis of the spine; pulmonary emphysema, with several dense nodules in the right hilar region; marked calcification of the aorta and the splenic artery; a sharply defined area of increased radiance over the left half of the diaphragm, interpreted as due to a congenital cyst of the lung, and a globular right kidney. Barium sulfate studies of the gastrointestinal tract on April 24 showed nothing significant; enlargement of the liver and the spleen were noted.

The electrocardiogram was normal, except for left axis deviation.

At the time of discharge from the hospital the patient had nocturia, with the passage of urine three to four times a night. This persisted for approximately three months and then decreased to once a night. Simultaneously albuminuria, moderate at all times, became persistently minimal. The blood nonprotein nitrogen level, elevated to 60 mg. per hundred cubic centimeters at the time of discharge

from the hospital, was normal two months later; the urea clearance was 99 per cent of normal five months after discharge.

Dyspnea recurred several months after discharge from the hospital but was relieved by digitalization. The liver remained palpable, but the spleen could not be felt after discharge, although roentgen examination showed it to be still enlarged.



Metabolism of hemoglobin during the attack of hemoglobinuria and during recovery. Note the greater excretion of hemoglobin in the urine when the patient was up and about during the seventh to the eighteenth day of the attack. The values for concentration of bilirubin in the plasma during the period when the concentration of hemoglobin in the plasma was above 30 mg. per hundred cubic centimeters are probably appreciably less than the actual amounts. Such discrepancy is discussed in the section on methods.

The patient reported that two months after the first episode of hemoglobinuria he passed bright red urine in the evening after a banquet and that he voided two progressively paler urines during the night and one at 6 a. m. which appeared normal in color. Since none of these urines were submitted to us for examination, it is impossible to evaluate the patient's observations.

OBSERVATIONS AND COMMENT

Hematologic Observations.—Hematologic studies made on the second day of illness, i. e., after two days of massive hemoglobinuria, revealed normal values (table 1). The red cell count was 4,710,000, the concentration of hemoglobin in the blood 94 per cent and the white cell count 10,100. With continuing hemoglobinemia and hemoglobinuria the red cell count and the concentration of hemoglobin in the blood gradually decreased to their lowest values of 2,920,000 and 59 per cent, respectively, on the fourteenth day after the onset of the attack. There was moderate reticulocytosis during this period. During the following week, when the hemoglobinemia and hemoglobinuria gradually disappeared, the red cell count and the concentration of hemoglobin in the blood increased somewhat, being 3,780,000 and 66 per cent, respectively, on the twenty-first day after the onset of the attack. The moderate reticulocytosis continued. The platelet count, white blood cell count and differential count were normal throughout the illness. Within two months after the termination of the attack the blood picture returned to normal (table 1).

Differential Diagnostic Studies.—This case of acute, severe hemoglobinuria, with jaundice and slowly developing anemia, occurring initially in a man aged 77, presented a difficult diagnostic problem. The attack was essentially asymptomatic. The slight burning on micturition experienced at times during the attack had also been experienced earlier and persisted during the follow-up period; nocturia was more frequent during the attack than before or after. There were no chills, fever, muscle pains, malaise, prostration or allergic manifestations. The onset of the attack was not associated with ingestion of drugs, fava beans or mushrooms; there was no history of exposure to toxic gases. Tests on the sixth and seventh days after the onset of the hemolytic attack showed no autoagglutinins on incubation of serum in the cold or at body or room temperature. The fragility of the red blood cells to hypotonic solutions of sodium chloride (table 1) and to lysolecithin was normal. The size and shape of the red blood cells appeared normal.

The clinical and laboratory findings in this case were compared with those in cases of recognized syndromes leading to hemoglobinuria in an attempt to make a differential diagnosis.

The history and findings ruled out hemoglobinuria due to infection, massive intraperitoneal hemorrhage and ingestion or inhalation of toxic substances.

TABLE 1.—*Hematologic Data During and After the Attack of Hemoglobinuria*

Date 1910	Day After Onset of Hemo- globinuria	Red Blood Cell Count, per Cu. Mm.	Blood Hemo- globin, Percentage	Hematocrit Reading, Percentage of Cells	Reticulo- cytes, Percentage	Platelets, per Cu. Mm.	White Blood Cell Count, per Cu. Mm.	Fragility to Hypotonic Solutions of Sodium Chloride	
								Minimum Resistance, Percentage of Sodium Chloride	Maximum Resistance, Percentage of Sodium Chloride
				During Attack					
4/22	3	4,710,000	94	44.0	10,100	44-40	26-24
4/23	4	4,630,000	91	2.3	409,000	10,300
4/24	5	4,220,000	81	1.8	8,700
4/25	6	4,050,000	76	2.4	7,000	46-40	26-24
4/26	7	3,710,000	73	34.8	5,500		
4/29	10	3,720,000	64	2.1	531,000	5,100		
5/ 1	12	3,320,000	63		
5/ 3	14	2,920,000	59	28.5	4,200		
5/ 5	16	3,060,000	60		
5/ 7	18	3,180,000	60	3.4	693,000	5,400		
5/10 *	21	3,780,000	66	1.4	560,000	7,200		
				Follow-Up Period					
5/20	..	3,540,000	63	29.3	2.7	389,000	7,400		
6/10	..	3,530,000	71	34.0	0.1	183,000	6,400		
6/24	..	4,600,000	77	37.5	7,300		
7/10	..	4,290,000	86	1.5	335,000	6,800		
10/30	..	5,020,000	91	43.9					

* End of attack.

That the pigmentation of the plasma and the urine was due to hemoglobin, and not to myoglobin, was established by spectrophotometric studies.¹⁵ Examinations of the plasma and the urine on the third day of illness revealed in each a point of maximum absorption at 575 millimicrons. This value agrees closely with the reported alpha band for human oxyhemoglobin,¹⁶ whereas the alpha band for oxymyoglobin is 581 millimicrons.¹⁷ Another point of maximum absorption was found in the plasma, and more faintly in the urine, at 619 millimicrons. This band shows the presence of methemalbumin, and its significance is discussed later. The clinical features of the attack in this case did not correspond in any way to those in an attack of myoglobinuria, which condition is characterized by muscle pains and stiffness, paralysis and extreme prostration and frequently terminates fatally.¹⁸

The findings did not correspond with those in attacks of paroxysmal hemoglobinuria of the chill or syphilitic type.¹² Reactions to Wassermann, Hinton and Kahn tests were negative. The Donath-Landsteiner test for cold hemolysins was negative on two examinations. Besides these negative laboratory data, the absence of symptoms and the long duration of the attack were further important criteria which ruled out the diagnosis of paroxysmal hemoglobinuria of the syphilitic type.

The diagnosis of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli disease)¹⁹ was excluded. An important criterion of this syndrome, as implied by the name, is marked exacerbation of hemolysis during sleep. In our patient the degree of hemoglobinuria was not greater during sleep than during waking hours (figure). Hemosiderinuria, which occurs constantly in cases of Marchiafava-Micheli disease,¹⁹ was not observed. The acid hemolysis test, diagnostic of Marchiafava-Micheli disease,¹³ gave negative results on repeated occasions. The absence of anemia and of jaundice prior to the onset of massive hemoglobinuria, the cessation of hemolysis after three weeks and the advanced age of the patient further ruled out Marchiafava-Micheli disease.

15. The spectrophotometric studies reported here were made by Dr. John F. Taylor, of the Biochemistry Department, Harvard Medical School. A Köning-Martens type of spectrophotometer was used.

16. Anson, M. L.; Barcroft, J.; Mirsky, A. E., and Oinuma, S.: On the Correlation Between the Spectra of Various Haemoglobins and Their Relative Affinities for Oxygen and Carbon Monoxide, *Proc. Roy. Soc., London*, s.B **97**:61, 1924.

17. Millikan, G. A.: Muscle Hemoglobin, *Physiol. Rev.* **19**:503, 1939.

18. (a) Hamburger, L. P., and Bernstein, A.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, *Am. J. M. Sc.* **192**:301, 1936. - (b) Millikan.¹⁷

19. Ham.¹³ Hamburger and Bernstein.^{18a}

Hemoglobinuria is observed not infrequently in cases of acute hemolytic anemia of the so-called Lederer type.²⁰ This condition occurs usually in children and in young adults; the hemolytic crisis is heralded by fever, vomiting, abdominal pain, somnolence and restlessness; the hemolysis results in severe anemia and jaundice, and there is usually marked leukocytosis. The advanced age of the patient in our case, the asymptomatic onset of the attack, the absence of fever and leukocytosis and the slow development of only moderate anemia are in contrast to the clinical picture in cases of typical acute hemolytic anemia of the Lederer type.

Hemoglobinuria rarely occurs in cases of chronic hemolytic jaundice.²¹ The clinical and laboratory data clearly preclude this diagnosis.

The findings in this case differed importantly from those in cases of march hemoglobinuria, in which condition paroxysmal attacks of hemoglobinuria occur in young men after short walks, long army pack marches or long strenuous runs.^{1b} Attacks may be repeatedly initiated over a period of a few years by a given exertion, or the condition may disappear completely after a few months. The paroxysms are usually unassociated with any symptoms. Hemoglobinuria usually lasts for only a few hours; in 1 unusual case the hemoglobinuria sometimes lasted for two or three days.²² Hematologic studies do not reveal anemia, reticulocytosis or any other abnormality. Physical examination in most instances yields nothing significant. After attacks the plasma bilirubin increases somewhat but not sufficiently to cause clinical icterus. The advanced age of our patient and the long duration of the attack of hemoglobinemia and hemoglobinuria, with development of moderate anemia and jaundice, were features markedly dissimilar to those in cases of march hemoglobinuria. Further, although hemolysis during the attack appeared to be exacerbated in this patient by exercise, as discussed later, no hemolytic attack could be initiated by having the patient walk considerable distances.

Bittorf²³ has reported several instances of hemoglobinuria occurring during attacks of acute glomerulonephritis. He found no hemoglobin in the plasma during the height of the hemoglobinuria in any of his patients. The patient whose condition is discussed here clearly did not fall into a group with these others.

20. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), *Medicine* **19**:231, 1940.

21. Batschwaroff, W.: Hämoglobinurie bei Icterus haemolyticus, *Deutsche med. Wchnschr.* **64**:191, 1938.

22. Foerster, A.: Ueber Marschhämoglobinurie, *München. med. Wchnschr.* **66**:554, 1919.

23. Bittorf, A.: Hämoglobinurische Nachschübe bei abklingender akuter hämorrhagischer Glomerulonephritis, *München. med. Wchnschr.* **68**:807, 1921.

The etiologic mechanism responsible for the hemolysis in this case was not suggested by any of the clinical or laboratory findings. The presence of occult blood in the stool during the height of the hemolytic attack was not considered due to a lesion of the gastrointestinal tract, but rather was ascribed to passage of hemoglobin from the plasma to the lumen of the bowel; a positive reaction for occult blood in the stool of a young adult patient with hemoglobinuria due to favism has been reported.²⁴ The persistence of the enlargement of the liver and the spleen during the six months of follow-up study since the disappearance of hemoglobinemia suggests that enlargement of these organs was not due entirely to the hemolytic attack. No diagnosis which would explain the enlargement of these organs could be established; it was felt, however, that cirrhosis of the liver was a possibility.

Metabolism of Blood Pigment.—The urine voided after admission to the hospital, twenty-four hours after the onset of the attack of hemoglobinuria, was dark burgundy red and contained 740 mg. of dissolved hemoglobin per hundred cubic centimeters; the plasma was dark red and contained 510 mg. of hemoglobin per hundred cubic centimeters. The plasma bilirubin was 1.5 mg. per hundred cubic centimeters²⁵ (figure), and slight icterus was noted. During the first twenty-four hours after admission a total of 8.7 Gm. of hemoglobin was excreted in the urine (figure).

During the first seven days of the attack the plasma and urine remained red (figure), the color decreasing gradually in intensity. On the seventh day, the concentration of hemoglobin in the plasma was 72 mg. per hundred cubic centimeters and the total urinary excretion of hemoglobin was 0.27 Gm., as compared with 8.7 Gm. on the first day after admission. The plasma bilirubin increased to 2.8 mg. per hundred cubic centimeters on the fourth day of the attack and decreased to 1.6 mg. on the seventh day (figure); the van den Bergh reaction was always indirect. Changes in the degree of jaundice approximately paralleled the levels of bilirubin. By the seventh day the red blood cell count had decreased to 3,700,000 per cubic millimeter (table 1). Blood destruction was further demonstrated by the abnormally high fecal urobilinogen excretion during this period (figure).

From the eighth to the eighteenth day the plasma was reddish brown and the concentration of hemoglobin varied around 30 mg. per hundred cubic centimeters. The urine contained much less hemoglobin

24. Hutton, J. E.: Favism: An Unusually Observed Type of Hemolytic Anemia, *J. A. M. A.* **109**:1618 (Nov. 13) 1937.

25. As stated in the section on methods, the values for plasma bilirubin are somewhat lower than actual in the presence of hemoglobinemia.

than on the previous days, the daily output ranging from 0.0 to 0.11 Gm. (figure). The red blood cell count further decreased to 2,920,000 per cubic millimeter on the fourteenth day and remained at approximately this level for the next four days (table 1). By the eighteenth day the bilirubin in the plasma had decreased to 0.8 mg. per hundred cubic centimeters and jaundice had disappeared. The fecal urobilinogen excretion remained elevated (figure). In this period blood destruction, although less marked than during the first six days, still continued, as evidenced by the persistence of hemoglobinemia and hemoglobinuria, by the further fall in the red cell count and concentration of hemoglobin in the presence of mild reticulocytosis and by the increased fecal urobilinogen excretion.

During the nineteenth to the twenty-second day evidences of abnormal hemolysis disappeared. The plasma hemoglobin was 8 mg per hundred cubic centimeters on the twenty-second day, a value within normal limits. The urine was completely free of hemoglobin from the twentieth to the twenty-second day. The fecal output of urobilinogen had decreased from the highest value of 416 mg. per day to one of 159 mg. per day (figure). Blood production was evidenced by the rise in the red cell count to 3,780,000 per cubic millimeter on the twenty-first day, by the increase in hemoglobin concentration to 66 per cent and by continued reticulocytosis (table 1).

Quantitative Estimation of the Extent of Intravascular Hemolysis Based on the Values for Plasma Hemoglobin.—The question arises whether the degree of intravascular hemolysis as indicated by the hemoglobinemia and hemoglobinuria was sufficiently great to cause anemia, jaundice and increased urobilinogen excretion.

Available data allow estimation of the amount of blood destruction required to maintain a given degree of hemoglobinemia. Hemoglobin in the plasma is destroyed gradually by the reticuloendothelial system, and at high levels of plasma hemoglobin some is excreted in the urine.²⁶ The rate of disappearance of hemoglobin from the plasma at varying levels of plasma hemoglobin after single intravenous injections of hemoglobin in normal persons has been studied recently in this laboratory.^{1a} The resultant data are applicable in ascertaining whether in a given patient with hemoglobinemia the hemoglobin is disappearing from the plasma at the rate expected if no more hemoglobin is being delivered to it or, if the hemolysis is continuing, the data allow estimation of the amount of hemoglobin which must be supplied to the

26. Ottenberg, R., and Fox, C. L., Jr.: The Rate of Removal of Hemoglobin from the Circulation and Its Renal Threshold in Human Beings, *Am. J. Physiol.* **123**:516, 1938. Gilligan, Altschule and Katersky.^{1a}

plasma to maintain a given degree of hemoglobin.²⁷ Unfortunately, the rate of disappearance of hemoglobin at blood levels of 500 mg. per hundred cubic centimeters was not measured after injections of hemoglobin in normal persons because we observed temporary untoward reactions even when levels of 300 to 400 mg. per hundred cubic centimeters were induced.²⁸ However, extension of the curve for the rate of disappearance of hemoglobin at lower levels of hemoglobin indicated that the concentration of plasma hemoglobin would decrease at a rate of about 75 mg. per hundred cubic centimeters per hour at a plasma hemoglobin level of 500 mg. per hundred cubic centimeters. This value includes the hemoglobin broken into its derived pigments and the hemoglobin excreted in the urine.

Since in this case the plasma hemoglobin level did not change appreciably from the second to the third day of the attack, it can be estimated that hemoglobin was being delivered to the plasma as fast as it was disappearing, namely, about 75 mg. per hour for each hundred cubic centimeters. This would amount in twenty-four hours, with the patient's estimated plasma volume of 2,150 cc.,²⁹ to 38.7 Gm. of hemoglobin, or the hemoglobin equivalent of 265 cc. of the patient's blood, as determined by the formula $\frac{38.7}{14.6} \times 100$, (table 2). Judging from the patient's history of passing "black" urine for the first twenty-four hours after

27. A small error giving slightly higher than actual values for blood destruction may be present in applying the data for the rate of disappearance of plasma hemoglobin after single intravenous injections of plasma hemoglobin in normal subjects to the data in a case of more long-standing hemoglobinemia. This possible error is noted because it has been shown that methemalbumin, which occurs together with oxyhemoglobin in the plasma of patients with hemoglobinuria of several days' duration or longer and which was present in our patient's plasma, disappears from the circulation less rapidly than oxyhemoglobin (Fairley³³).

From this same source a small error giving slightly lower than actual values for blood destruction may be present in calculations based on the fecal urobilinogen excretion, since available evidence indicates that methemalbumin is excreted by the liver, the prosthetic group probably appearing in the feces as a porphyrin (Rimington, C.: *Porphyrins and Their Relation to the Metabolism of Blood Pigments*, Proc. Roy. Soc. Med. **32**:1268, 1939).

28. Footnote 1a. Hemoglobin disappeared from the plasma at the average rate of 10 mg. per hundred cubic centimeters of plasma per hour at an average plasma hemoglobin level of 30 mg. per hundred cubic centimeters and at rates of 28 and 47 mg. per hundred cubic centimeters per hour at average plasma hemoglobin levels of 99 and 201 mg. per hundred cubic centimeters, respectively.

29. The plasma volume was estimated from the blood volume (calculated from the data of Gibson and Evans¹⁴) and from the patient's hematocrit value of 44 per cent. The plasma volume probably increased somewhat during the later periods, when the hematocrit reading was approximately 30 per cent; for purposes of simplicity the initial calculated plasma volume is used throughout these calculations.

the onset of the attack, i. e., before admission to the hospital, and from the observations on admission that the plasma bilirubin was already elevated and mild jaundice was present, we estimated that the blood destroyed during the first day of the attack was at least as much as that destroyed on the second day of the illness. On the third day after the beginning of the attack the plasma hemoglobin decreased to 360 mg. per hundred cubic centimeters, an indication that hemolysis was somewhat less severe and that the plasma hemoglobin was decreasing at a rate of 6 mg. per hour per hundred cubic centimeters of plasma. The average estimated amount of hemoglobin delivered to plasma for this day, calculated from the mean blood hemoglobin value between 500 and 360 mg., namely, 430 mg., according to the formula $\frac{68 \times 21.50 \times 24}{1,000}$, is 35.1 Gm., the equivalent of 244 cc. of blood of the blood hemoglobin level of the patient for the day. The fourth to the sixth day after the onset of the attack the level of the plasma hemoglobin decreased from 360 to 122 mg. per hundred cubic centimeters, an average rate of disappearance of 5 mg. per hundred cubic centimeters per hour. To maintain the mean plasma level of 240 mg. per hundred cubic centimeters approximately 52 mg. of hemoglobin per hundred cubic centimeters per hour would have to be delivered to the plasma. Daily hemolysis for these two days may be estimated according to the foregoing method as equivalent to approximately 200 cc. of the patient's blood (table 2). Similar calculations based on the findings from the sixth to the twentieth day, inclusive, of the attack revealed a total hemolysis equivalent to the hemoglobin content of 880 cc. of the patient's blood.

In summary, it is estimated that the red cells of approximately 2,000 cc. of blood were destroyed intravascularly during the entire hemolytic attack (table 2). During the first fourteen days of the attack, when the red blood cell count and concentration of hemoglobin decreased from 4,710,000 and 94 per cent to 2,920,000 and 59 per cent respectively, the data show destruction of the red cells of 1,850 cc. of the patient's blood. It seems justifiable to conclude from these data that the degree of hemolysis which occurred intravascularly was sufficient to cause the anemia.

Quantitative Estimation of the Extent of Hemolysis Based on Fecal Urobilinogen Excretion.—Unfortunately, the stools representing the first three days of the attack were not available; a stool obtained after an enema on the morning of the fourth day of the attack was discarded and the collection period began from this time. Defecation was regular and daily throughout the period of study; the average weight of the daily stool was 90 Gm.

The hemoglobin and the blood equivalents of the excess of urobilinogen over that to be expected for normal hemoglobin catabolism were calculated according to Watson's method.³⁰ Watson estimated that normally 0.46 per cent of the hemoglobin of the blood was excreted daily as urobilinogen. The hemoglobin equivalent of the urobilinogen is estimated from the formula: 41.8 mg. of urobilinogen \approx 1 Gm. of hemoglobin. The total fecal urobilinogen excretion for the nineteen days of the study, from the fourth to the twenty-second day, inclusive, after the onset of the attack (figure) was 6,000 mg. With the average

TABLE 2.—*Total Amount of Hemolysis Occurring During the Attack of Hemoglobinuria, as Estimated from the Values for Plasma Hemoglobin*

Day After Onset of Hemoglobinuria	Amount of Hemolysis, Gm. of Hemoglobin	Hemoglobin in Whole Blood, Gm. per 100 Cc.	Volume of Blood Destroyed, Cc.
1	38.7 *	265 *
2	38.7	265
3	35.1	14.6	245
4	26.8	14.2	205
5	26.8	12.6	210
6	14.3	11.8	125
7	11.4	11.4	100
8	8.3	11.0	80
9	8.3	80
10	5.2	10.0	55
11	5.2	55
12	5.2	9.8	55
13	5.2	55
14	5.2	9.2	55
15	5.2	55
16	5.2	9.3	55
17	3.6	40
18	3.6	9.3	40
19	1.5	15
20	1.5	15
21	0.0	10.3	0
22	0.0	0
Total.....	255.0		2,070

* The concentration of hemoglobin in the plasma on the first day of the attack, before admission to the hospital, was not obtained. As discussed in the text, hemolysis was probably at least as great on this day as on the one following.

hemoglobin value of 10.4 Gm. per hundred cubic centimeters of blood for the entire period and the calculated blood volume of 4,700 cc., the circulating hemoglobin was 490 Gm. According to Watson's value of 0.46 per cent, this total blood hemoglobin would normally result in a daily excretion of 95 mg. of urobilinogen ($490 \times \frac{0.46}{100} \times 41.8 = 95$ mg.), or 1,790 mg. for the nineteen days of study. There was, therefore, 4,210 mg. of urobilinogen in excess of the expected amount under

30. Watson, C. J.: The Pyrrol Pigments, with Particular Reference to Normal and Pathologic Hemoglobin Metabolism: IV. Rate of Hemoglobin Metabolism, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2506.

conditions of normal hemoglobin catabolism. This amount of urobilinogen is equivalent to 101 Gm. of hemoglobin ($\frac{4,210}{41.8}$), or the hemoglobin of approximately 1,000 cc. of the patient's blood, with an average hemoglobin concentration of 10.4 Gm. per hundred cubic centimeters. This figure of 1,000 cc. of blood destroyed during the fourth to the twenty-second day, inclusive, of the attack as calculated by this method is to be compared with the value of 1,300 cc. of blood destroyed as calculated from the plasma hemoglobin values for the same period.

The finding that the amount of blood destroyed as calculated from the urobilinogen excretion was not greater than the amount destroyed as calculated from the values for plasma hemoglobin demonstrated that the blood destruction was entirely "intravascular," i. e., that the hemoglobin from the blood destroyed was liberated into the circulation. This is in contrast to the findings in cases of well recognized types of hemolytic crises, in which severe anemia may develop rapidly without the appearance in the circulation of any, or sometimes only a small amount, of the hemoglobin of the blood destroyed.³¹

Nature of the Hemoglobin Pigments of Plasma and Urine.—As noted previously, spectrophotometric studies on the third day of the attack revealed oxyhemoglobin in both the plasma and the urine, and in addition, a band at 619 millimicrons in the plasma and a similar faint band in the urine. There was no methemoglobin either in the plasma or in the urine. An absorption band at 576 millimicrons and one at approximately 620 millimicrons were observed with a Zeiss hand spectroscope in several samples of plasma during the following ten days. From the sixth to the sixteenth day after the onset of the attack, when the plasma hemoglobin according to the benzidine reaction was 122 to 30 mg. per hundred cubic centimeters, the plasma showed a reddish brown to brownish discoloration rather than the red discoloration which we have observed in man at similar levels of plasma hemoglobin after intravenous injections of solutions of hemoglobin and in attacks of march hemoglobinuria. The urine, on the other hand, showed only oxyhemoglobin with a hand spectroscope and was more reddish than the plasma even when the urinary concentration of hemoglobin, according to the benzidine reaction, was less than that of the plasma.

The brownish discoloration of the plasma and the absorption band at 619 millimicrons demonstrated the presence of methemalbumin, a brown pigment which has been described only recently.³² Using a

31. Gilligan, D. R., and Kapnick, I.: Clinical and Laboratory Observations on Hemoglobinuria Occurring During Sulfanilamide Therapy, *New England J. Med.* **224**:801, 1941. Dameshek and Schwartz.²⁰

32. Fairley, N. H.: Methaemalbumin in Man (Pseudo-Methaemoglobin), *Proc. Roy. Soc. Med.* **32**:1278, 1939.

Hartridge reversion spectroscopie, Fairley³³ found the point of maximum absorption of the alpha band of this pigment at 623 millimicrons, and Heilmeyer,³⁴ using a Köning-Martens type of spectrophotometer, which we also employed in our studies, found the point of maximum absorption of the alpha band at 620 millimicrons. Methemalbumin apparently occurs in the plasma when the hemoglobin molecule in the circulation is split into heme and globin and the heme is oxidized to hematin, which promptly unites with the crystalalbumin of the plasma.³² Ham³⁵ and we too have noted this brownish discoloration of the plasma in patients with Marchiafava-Micheli disease when the concentration of hemoglobin, as measured by the benzidine test, was between 25 and 60 mg. per hundred cubic centimeters. Fairley³² has identified methemalbumin by spectrophotometric examination of the plasma of patients with blackwater fever, those with paroxysmal nocturnal hemoglobinuria and those experiencing transfusion reactions. An absorption maximum at approximately this same wavelength also has been reported to be present in the serum in some other hemolytic conditions.³⁶ This pigment was not observed on spectrophotometric analysis of the plasma of patients with march hemoglobinuria recently studied in this laboratory.^{1b} We have never noted this brownish discoloration of the plasma in cases of hemoglobinemia following intravenous injection of 1.5 to 16.0 Gm. of hemoglobin^{1a} or during either the hemoglobinemia of march hemoglobinuria^{1b} or the physiologic hemoglobinemia occasioned in normal subjects by long runs.³⁷ Apparently, methemalbumin is found only in cases of a higher degree of hemoglobinemia or of more prolonged hemoglobinemia in which some of the hemoglobin remains in the circulation for a considerable period; the presence of this pigment is, therefore, of no diagnostic significance.

Effect of Exercise on Hemoglobinemia and Hemoglobinuria in Our Patient and in a Patient with Marchiafava-Micheli Disease.—By the seventh day after the onset of the attack our patient's hemoglobinuria had subsided markedly, so that the urine was straw colored and showed

33. Fairley, N. H.: The Fate of Extracorporeal Circulating Hemoglobin, *Brit. M. J.* **2**:213, 1940.

34. Heilmeyer, L.: *Medizinische Spectrophotometrie*, Jena, Gustav Fischer, 1934, p. 121.

35. Ham, T. H.: Personal communication to the authors.

36. Schumm, O.: Ueber den Nachweis von Hämatin im menschlichen Blutserum, *Ztschr. f. physiol. Chem.* **87**:171, 1913. Feigl, J.: Ueber das Auftreten von Hämatin im Blute bei Vergiftung mit Chloraten, *Biochem. Ztschr.* **74**:394, 1916; *Chemische Blutuntersuchungen an der Teilnehmern eines Armes-Gepäckmarsches. I. Ueber Umsatz und Ausscheidung von Blutfarbstoff. Hämoglobinämie, Hämatinämie und Hämoglobinurie*, *ibid.* **76**:88, 1916.

37. Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Unpublished data.

only a small concentration of hemoglobin, according to the benzidine test. The plasma hemoglobin level had decreased to 70 mg. per hundred cubic centimeters (figure). The patient was for the first time allowed to be up and about the ward for some hours, whereupon the urine again became pink. The average concentration of the urinary hemoglobin for this day was 20 mg. per hundred cubic centimeters. The patient remained in bed on the following two days. The plasma hemoglobin decreased during this period to 31 mg. per hundred cubic centimeters. On the morning of the tenth day the urine was free of hemoglobin, but after the patient had been up and about the ward for a short period the urine again showed a trace of hemoglobin.

The suggestion afforded by these observations, that the hemolytic process was exacerbated by exertion, was further tested by having the patient walk 0.5 mile (0.8 kilometer) in thirteen minutes. On this exertion, the plasma hemoglobin increased from 31 to 50 mg. per hundred cubic centimeters and the urine became light red and showed concentrations of hemoglobin up to 51 mg. per hundred cubic centimeters (table 3). The hemoglobin in the urine then decreased to an immeasurable trace in the following three hours of rest in bed. Two days later the walk was repeated, with similar results. Several days later, when the plasma hemoglobin was 28 mg. per hundred cubic centimeters, it was demonstrated that standing still in the upright position also evoked a small increase in plasma hemoglobin and slight hemoglobinuria (table 3). On the nineteenth day after the onset of the attack, when the plasma hemoglobin had decreased to 12 mg. per hundred cubic centimeters, standing no longer evoked appreciable hemoglobinemia or hemoglobinuria, and two days later, when the plasma hemoglobin had become normal, a walk of 1.1 miles (1.7 kilometer) in thirty minutes produced neither hemoglobinemia nor hemoglobinuria (table 3). The same exertion ten days later, and again several months later, also failed to produce hemolysis.

In connection with these findings demonstrating increased hemolysis on exercise during the hemolytic attack, the question arises whether a patient with hemoglobinemia from any cause may likewise show increased hemolysis on exercise. Data concerning this question are meager. In patients with Marchifava-Micheli disease and constant hemoglobinemia exacerbation of hemolysis does not occur during the day, but rather there is partial recovery from the hemolytic attacks which occur during sleep.¹³ We have had the opportunity to study the effect of exercise on the degree of hemolysis in a patient with Marchiafava-Micheli disease referred to us by Dr. Ham. The data for this patient showed no effect of exercise on the amount of hemoglobin in the plasma or the urine (table 3). It was fortunate that the

TABLE 3.—Effect of Walking and of Posture on Degree of Hemoglobinemia and Hemoglobinuria in Patient (J. Y.) Reported on Here and in a Patient (L. G.) with Marchiafava-Micheli Disease

Patient	Date	Day After Onset of Hemoglobinuria	Time	Condition of Patient During Study	Plasma Hemoglobin, Mg./100 Cc.	Urine		
						Concentration, Mg./100 Cc.	Excreted, Mg./Hr.	"Albumin,"* Mg./100 Cc.
J. Y.	4/29	10	5:30 a.m. - 7:00 a.m.	In bed.....	31	0	Trace	44
			7:00 a.m. - 12:15 p.m.	In chair.....	50	31	9	..
			12:15 p.m. - 1:15 p.m.	Walking 0.5 mile in 13 min.....	..	51	33	201
			1:15 p.m. - 2:15 p.m.	In chair.....	..	21	26	..
	5/ 1	12	2:15 p.m. - 4:45 p.m.	In bed.....	..	Trace	Trace	14
			4:45 p.m. - 4:30 a.m.	In bed.....	..	0	0	..
			4:30 a.m. - 6:00 a.m.	In bed.....	..	0	0	6
			7:20 a.m. - 9:15 a.m.	In bed.....	26	7	7	..
	5/ 2	13	9:15 a.m. - 10:45 a.m.	Up and about ward.....	39	24	16	336
			10:45 a.m. - 11:15 a.m.	Walking 0.5 mile in 11 min.....	..	16	8	..
			11:15 a.m. - 12:30 p.m.	In bed.....	..	2	4	..
			12:30 p.m. - 2:30 p.m.	In bed.....	..	Trace	Trace	..
	5/ 6	17	2:30 p.m. - 4:30 p.m.	In bed.....	..	Trace	Trace	..
			6:00 a.m. - 10:00 a.m.	In bed and up.....	40	11	10	239
			10:00 a.m. - 2:00 p.m.	Up and about ward.....	..	8	6	..
			2:00 p.m. - 6:00 p.m.	Up and about ward.....	..	1	1	..
L. G.	5/ 8	19	6:00 p.m. - 2:00 a.m.	Up and to bed.....	..	Trace	Trace	..
			10:00 p.m. - 2:00 a.m.	In bed.....	..	Slight trace	Trace	114
			2:00 a.m. - 6:00 a.m.	In bed.....	22
			10:00 a.m.	In bed.....	..	3	3	75
	5/10	21	10:13 a.m. - 1:25 p.m.	In chair.....	28	3	1	..
			1:25 p.m. - 2:35 p.m.	In chair.....	35	12	11	..
			2:35 p.m. - 3:20 p.m.	Standing upright 30 min.....	..	24	12	172
			3:20 p.m. - 5:10 p.m.	In chair.....	..	13	11	..
	5/20	31	5:10 p.m. - 7:00 p.m.	In chair.....	..	Trace	Trace	..
			7:00 p.m. - 5:00 a.m.	In bed.....	..	0	0	..
			5:00 a.m. - 7:00 a.m.	In bed.....	..	Trace	Trace	..
			10:15 a.m. - 1:25 p.m.	In chair.....	12	4	6	178
	5/26	129	1:25 p.m. - 2:05 p.m.	In chair.....	14	5	5	141
			2:05 p.m. - 3:05 p.m.	Standing in a kyphotic position 30 min.....	15	Slight trace	Slight trace	133
			3:05 p.m. - 3:53 p.m.	Standing upright 30 min.....	..	Slight trace	Slight trace	..
			3:53 p.m. - 7:00 p.m.	In chair.....	..	0	0	..
L. G.	6/11	..	7:00 p.m. - 7:00 a.m.	In bed.....	8	0	0	48
			7:00 a.m. - 8:30 a.m.	In bed.....	8	0	0	50
			8:30 a.m. - 9:45 a.m.	Walking 1.1 mile in 30 min.....	7	0	0	295
			9:45 a.m. - 10:45 a.m.	Walking 1.1 mile in 30 min.....	6	0	0	250
L. G.	6/11	..	10:00 a.m. - 10:45 a.m.	Walking 1.1 mile in 30 min.....	5	0	0	..
			8:00 a.m. - 9:15 a.m.	Traveling on train.....	29	4 †	3	..
			9:15 a.m. - 10:30 a.m.	In bed (awake).....	28	0	0	50
			10:30 a.m. - 11:15 a.m.	Walking 1.5 mile in 30 min.....	30	0	0	40

* The urine "albumin" represents the total protein value minus the hemoglobin value.

† The first urine voided in the morning, at 7 a. m., contained 58 mg. of hemoglobin per hundred cubic centimeters.

concentration of plasma hemoglobin before exercise in this patient was almost identical with that obtained before the exercise which produced hemoglobinuria in our patient.

The exacerbation of hemolysis by exercise occurring during the hemolytic attack in our patient is not characteristic, therefore, of all syndromes with intravascular hemolysis.

Renal Function.—The nonprotein nitrogen level of the blood was elevated to 90 mg. per hundred cubic centimeters on the day after admission. The creatinine content of the blood was 3.2 mg. per hundred cubic centimeters, and the total plasma protein, 6.7 Gm. per hundred cubic centimeters. The corrected sedimentation index was 0.61. The nonprotein nitrogen gradually decreased to 62 mg. per hundred cubic centimeters a week after admission and remained at approximately this level during the following two weeks of the attack. The volume of urine when fluid was forced during the attack was approximately 2,000 cc. per twenty-four hour period, with slightly larger values at night than during the day; the specific gravity of the day and the night specimens and of many individual specimens during twenty-four hour periods varied only between 1.008 and 1.012. The urine contained protein throughout the three weeks of the attack, in amounts related to the degree of hemoglobinuria. During severe hemoglobinuria the "albumin"³⁸ output (i. e., total protein minus hemoglobin) was 5 to 6 Gm. a day (figure); subsequently, when hemoglobin was absent from the urine or was present only in traces, the daily "albumin" output was 0.3 to 1.3 Gm. (figure). The urinary sediment showed a few red and a few white blood cells and rare brown granular casts. The urine was maintained alkaline throughout the period of massive hemoglobinuria. The amount of urinary sediment was always small; repeated examination failed to reveal any hemoglobin casts or hemosiderin granules. The urea clearance was 20 per cent of normal, with a blood urea nitrogen value of 44 mg. per hundred cubic centimeters, on the third day after admission. On the sixteenth day the clearance was 19 per cent of normal, with a blood urea nitrogen value of 28 mg. per hundred cubic centimeters.

During the two months after the end of the attack the nonprotein nitrogen value decreased to 33 mg. per hundred cubic centimeters and remained between this level and 40 mg. per hundred cubic centimeters during the remainder of the follow-up study. The urea clearance six months after the attack was 99 per cent of normal, with a blood urea nitrogen value of 13.5 mg. per hundred cubic centimeters. There was only a slight trace of albumin in the urine (12 mg. per hundred cubic centimeters) at this time, and the urinary sediment showed, as on all previous occasions, only small numbers of formed elements.

38. No studies were made to identify the nature of this protein fraction.

The temporary reduction of renal function in this patient was interpreted as secondary to the hemolytic attack; the clinical and laboratory findings did not suggest any primary acute renal disease. Fairley and Bromfield³⁹ consistently observed rises in blood urea and either polyuria or oliguria in patients with the hemoglobinuria of blackwater fever; in the patients who recovered, the blood urea returned to normal a few days to two weeks after cessation of hemoglobinuria. Studies of urea clearance during hemoglobinuria due to intravenous injection of hemoglobin and during march hemoglobinuria showed no reduction in renal function¹; the hemoglobinuria, however, in these instances was neither of as great a degree nor of as long a duration as in this case. In cases of Marchiafava-Micheli disease, with hemoglobinemia and hemoglobinuria persisting for several years, renal function is markedly reduced; constant hemosiderinuria is observed in such instances. The absence of hemoglobin casts and the sparsity of all types of casts in this patient's urine show that significant tubular obstruction was not present; it is to be remembered that the urine was maintained alkaline to prevent precipitation of hemoglobin products in the tubules.

Hepatic Function.—The liver of this patient was palpable, appeared enlarged on roentgenographic examination during the time of the hemolytic attack and remained enlarged during the period of follow-up study.

Bilirubinemia and moderate jaundice resulted from the hemolytic attack. The amount of intravascular hemolysis was considered great enough to explain the temporary increase in plasma bilirubin without invoking impaired hepatic function as the cause; with an associate,^{1a} we have previously shown that the plasma bilirubin increased in normal subjects after single intravenous injections of amounts of hemoglobin which induced lower plasma hemoglobin concentrations than the levels present in this patient during the first four days of the hemolytic attack. The question has been raised in the past whether jaundice can occur in hemolytic crises solely because of overproduction of bilirubin or whether icterus results both from increased bilirubin production and from decreased excretory capacity of the liver for bilirubin. In many hemolytic crises, severe anemia and jaundice develop rapidly and simultaneously, so that anoxia is present at the time the level of bilirubin is elevated; the relative importance of the blood destruction itself and of anoxia and its possible effect on hepatic function in the causation of bilirubinemia cannot be evaluated in such instances. In this case jaundice developed in the absence of anemia. As the rate of hemolysis decreased, the plasma bilirubin promptly returned to normal. The

39. Fairley, N. H., and Bromfield, R. J.: Laboratory Studies in Blackwater Fever: III. A New Blood Pigment in Blackwater Fever and Other Biochemical Observations, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:307, 1934.

absence during the height of the jaundice of bile in the urine, the normal urinary urobilinogen, i. e., 1 to 4 mg. per day, and the plasma cholesterol value of 297 mg. per hundred cubic centimeters, with 40 per cent esters, afforded additional evidence that the hepatic function was normal.

SUMMARY

A case of acute, massive hemoglobinemia and hemoglobinuria of obscure cause, in which moderate jaundice and anemia developed, is reported. Hemoglobinemia and hemoglobinuria were greatest during the first days after the onset of the attack and continued for approximately three weeks.

The red blood cell count decreased during the first two weeks of the attack from 4,710,000 to 2,900,000 and the concentration of hemoglobin in the blood decreased from 94 to 59 per cent. Clinical jaundice increased during the first four days of the attack and then gradually disappeared during the following week.

The spleen and the liver were enlarged during the attack; subsequently the size of the spleen decreased slightly. Renal function was reduced during the attack and subsequently returned to normal. Hepatic function was normal.

Oxyhemoglobin and methemalbumin were identified spectrophotometrically in the plasma. The urinary pigment was chiefly oxyhemoglobin.

Quantitative studies of the hemoglobin of the plasma and the urine and quantitative studies of the fecal output of urobilinogen revealed the extent of hemolysis during the attack. Calculations based on the values for hemoglobin in the plasma and in the urine indicated hemolysis of the red cells of approximately 1,400 cc. of the patient's blood during the first week of the attack, of 400 cc. during the second week and of 200 cc. during the third.

Calculations based on excretion of urobilinogen in the stools collected from the fourth to the nineteenth day after the onset of hemoglobinuria indicated hemolysis of approximately 1,000 cc. of blood during this period, as compared with hemolysis of approximately 1,300 cc. for the same period as calculated from the values for plasma hemoglobin.

The slow development of moderate anemia and moderate jaundice accorded with the amount of blood destruction represented by these calculations. The correspondence between the amounts of blood destroyed during the attack as calculated from the values for plasma hemoglobin and from the total urobilinogen excretion demonstrated that all of the hemoglobin from the blood destroyed during the attack was released into the circulation. This situation is contrasted with

that in the hemolytic attacks occurring in some conditions in which more severe anemia develops with greater rapidity and yet in which there may be no evidences of "intravascular" hemolysis.

During the later stages of the hemolytic attack in this patient it was demonstrated that walking caused a definite but slight exacerbation of hemolysis; after the end of the attack, hemolysis could not be induced by walking or by standing. Exacerbation of hemolysis on walking did not occur in a patient with Marchiafava-Micheli disease with associated hemoglobinemia.

The clinical manifestations and the laboratory findings in this case were not typical of those in any recognized type of hemolytic attack. No autoagglutinins could be demonstrated in the blood of this patient when tests were made on serum incubated in the cold or at body or room temperature. The fragility of the red cells to hypotonic solutions of sodium chloride was normal. The differential diagnosis of hemoglobinuria is discussed.

Progress in Internal Medicine

DISEASES OF THE ADRENAL GLANDS

I. ADDISON'S DISEASE

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Since one of us (E. J. K.)¹ reviewed for this journal the literature dealing with the diseases of the adrenal glands remarkable progress has been made. Crystalline compounds of known chemical structure have been isolated from the adrenal cortex, and one of these subsequently has been synthesized. The pharmacologic properties of many of these substances have been delineated in detail. As a result the treatment of Addison's disease has improved greatly. Better methods for the recognition of Addison's disease have been developed. The ramifications of the physiologic abnormalities of adrenal cortical insufficiency have been explored further. Knowledge of the relation of the adrenal cortex to the constellation of physiologic processes which pertain to sex has been materially advanced, and, in addition, many experimental studies which are concerned with "interglandular relations" have been conducted. Finally, the therapeutic potentialities of adrenal cortical substances for the treatment of disorders which are not primarily adrenal in origin have been investigated and the results reported. In each of these broad fields of endeavor many isolated bits of factual material have been gathered which at present cannot readily be inserted into the general mosaic. These we have deliberately ignored, not, however, without considerable misgiving.

An all-embracing review of this material would be of little value to most clinicians. We therefore decided to limit our survey to the literature which appeared to have clinical significance at present or which promised to have a bearing on clinical problems in the not too distant future. However, in dealing with the pathologic physiology of adrenal

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1. Kepler, E. J.: Diseases of the Adrenal Glands: A Review with Special Reference to the Clinical Aspects, *Arch. Int. Med.* **56**:105-135 (July) 1935.

cortical insufficiency it was necessary often to deviate from this criterion. Consequently, considerable space is devoted to studies in which experimental animals were used. Whether the results that were obtained from such studies are directly applicable to clinical medicine remains to be seen. In many instances we can be reasonably safe in assuming that they are not. Considerable attention also was given to certain work involving fundamental principles of electrolyte and water metabolism. Whether these studies should have been reviewed at this particular time for this particular journal was a moot question. This material was included because clinicians generally have not appreciated its significance and also because it bears directly on other pathophysiologic processes comparable to those which are encountered in adrenal cortical insufficiency. After all, the continued interest of clinicians in diseases of the adrenal glands arises largely from the fact that in a sense they are key disorders, the understanding of which would illuminate many of the perplexing problems which arise in everyday medical practice.

Our review, then, is distinctly selective rather than comprehensive. In the preparation of any review of this type the personal interests, tastes and prejudices of the authors usually insert themselves. This cannot be avoided; nevertheless, we apologize for it.

PATHOLOGY OF ADDISON'S DISEASE

In 1934 Snell² called attention to the fact that the incidence of adrenal cortical atrophy (in comparison with tuberculosis) as a cause of fatal Addison's disease appeared to be increasing. More recently Cragg³ and Wells and his associates⁴ have observed that this trend persists. The latter authors suggested that the widespread use of drugs which have been introduced in recent years may be responsible for the apparent increase of adrenal cortical atrophy. They cited 2 instances in which adrenal cortical atrophy occurred in patients who were treated for pemphigus by the administration of germanin. Talbott and associates⁵ criticized the inferences drawn by Wells and his co-workers and

2. Snell, A. M.: The Treatment of Addison's Disease, *Proc. Staff Meet., Mayo Clin.* **9**:57 (Jan. 24) 1934.

3. Cragg, R. W.: Personal communication to the authors.

4. Wells, H. G.: Addison's Disease with Selective Destruction of the Suprarenal Cortex, *Arch. Path.* **10**:499-523 (Oct.) 1930. Wells, H. G.; Humphreys, E. M., and Work, E. G.: Significance of the Increased Frequency of Selective Cortical Necrosis of the Adrenal as a Cause of Addison's Disease, *J. A. M. A.* **109**:490-493 (Aug. 14) 1937.

5. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus in Relation to Effects of Cortical Extract and Sodium Chloride, *J. Invest. Dermat.* **3**:31-68 (Feb.) 1940.

called attention to 2 cases of pemphigus in which associated adrenal cortical hemorrhages were observed at necropsy. They implied that the lesions described by Wells may have been the result of the pemphigus per se.

The apparently increased incidence of adrenal cortical atrophy at necropsy does not necessarily imply that this condition is actually on the increase. If the incidence of tuberculosis of the adrenal cortex is decreasing or if the length of life of patients having this condition is being extended, the incidence of adrenal cortical atrophy at necropsy would be relatively increased. Irrespective of its interpretation, the fact remains that Snell, Cragg and Wells all have found that cortical atrophy now accounts for about half of the cases of fatal Addison's disease, whereas formerly tuberculosis was the etiologic factor in about 90 per cent of cases.

PATHOLOGIC PHYSIOLOGY

Interest in the pathologic physiology of adrenal cortical insufficiency continues to center chiefly on electrolyte metabolism, renal dysfunction and carbohydrate metabolism.

Electrolyte Metabolism.—Sodium: Loeb,⁶ in 1932, observed an unusually low concentration of sodium and chloride in the serum of 3 patients who had Addison's disease. One of these patients was benefited by the administration of large amounts of sodium chloride and remained in a state of reasonably good health for five months. At this time the appearance of peripheral edema led to the discontinuance of treatment with sodium chloride, and a crisis of adrenal cortical insufficiency was precipitated.⁷ The latter report stimulated a tremendous interest in the relation of the adrenal cortex to the metabolism of electrolytes.

From experimental observations on dogs and rats, it was evident⁸ that after adrenalectomy the excretion of sodium and chloride in the urine was increased. This was prevented by administration of a crude extract of the adrenal cortex.^{8b} Since the loss of sodium appeared to be

6. Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, *Science* **76**:420-421 (Nov. 4) 1932.

7. Loeb, R. F.: Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease, *Proc. Soc. Exper. Biol. & Med.* **30**:808-812 (March) 1933.

8. (a) Loeb, R. F.; Atchley, D. W.; Benedict, E. M., and Leland, J.: Electrolyte Balance Studies in Adrenalectomized Dogs with Particular Reference to the Excretion of Sodium, *J. Exper. Med.* **57**:775-792 (May) 1933. (b) Harrop, G. A.; Soffer, L. J.; Ellsworth, R., and Trescher, J. H.: Studies on the Suprarenal Cortex: III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, *ibid.* **58**:17-38 (July) 1933. (c) Rubin, M. I., and Krick, E. T.: The Salt and Water Metabolism of Adrenal Insufficiency and Partial Starvation in Rats, *J. Clin. Investigation* **15**:685-695 (Nov.) 1936.

of greater magnitude than that of chloride,⁹ it was suggested that the adrenal cortex primarily influenced the metabolism of sodium.¹⁰

Efforts to compensate for this unusual excretion of sodium and chloride by administration of sodium chloride, either alone or in conjunction with sodium bicarbonate, resulted in prolongation of the lives of adrenalectomized animals. This treatment, however, was not accompanied by return of a completely normal pattern of electrolytes in the plasma, and the animals eventually died. Swingle¹¹ concluded from this that sodium chloride alone was not a complete substitute for extracts of the adrenal cortex in the treatment of adrenalectomized animals.

Potassium: The metabolism of potassium also appears to be disturbed in cases of adrenal cortical insufficiency. That the concentration of this ion increases in the plasma of animals dying in crisis has been known for some time.¹² This increase in concentration apparently is related to decreased excretion of potassium by the kidney.¹³ Conversely, recovery from adrenal cortical insufficiency is associated with the excretion of unusually large amounts of potassium in the urine. Analysis of tissue¹⁴ removed from adrenalectomized animals suggested that the increase in the concentration of potassium in the serum is associated with a simultaneous increase in the content of potassium both in the interstitial fluid and in the cells themselves.¹⁴ This has been interpreted as a passive response to the retention of potassium, which the kidney appears unable to excrete.

9. Such a loss might have been anticipated in view of the fact that blood plasma and interstitial fluids contain more sodium than chloride.

10. (a) Harrop, G. A.; Soffer, L. J.; Nicholson, W. M., and Strauss, M.: Studies on the Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, *J. Exper. Med.* **61**:839-860 (June) 1935. (b) Allers, W. D.: The Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, *Proc. Staff Meet., Mayo Clin.* **10**:406-409 (June 26) 1935. (c) Loeb and others.^{8a}

11. Swingle, W. W.; Pfiffner, J. J.; Vars, H. M., and Parkins, W. M.: The Effect of Sodium Chloride Administration upon Adrenalectomized Dogs Not Receiving Extract, *Am. J. Physiol.* **108**:159-167 (April) 1934.

12. Hastings, A. B., and Compere, E. L.: Effect of Bilateral Suprarenalectomy on Certain Constituents of the Blood of Dogs, *Proc. Soc. Exper. Biol. & Med.* **28**:376-378 (Jan.) 1931.

13. Harrop, G. A.; Nicholson, W. M., and Strauss, M.: Studies on the Suprarenal Cortex: V. The Influence of the Cortical Hormone upon the Excretion of Water and Electrolytes in the Suprarenalectomized Dog, *J. Exper. Med.* **64**:233-251 (Aug.) 1936.

14. Harrison, H. E., and Darrow, D. C.: The Distribution of Body Water and Electrolytes in Adrenal Insufficiency, *J. Clin. Investigation* **17**:77-86 (Jan.) 1938.

The significance of the dietary intake of potassium was emphasized first by Allers, Nilson and Kendall.¹⁵ They and others¹⁶ found that adrenalectomized dogs treated with sodium salts could be maintained indefinitely with normal concentrations of electrolytes in the plasma if the intake of potassium was restricted. This situation was in contrast to the difficulties often encountered when the content of potassium in the diet was disregarded.¹⁷ The clinical significance of these observations has been emphasized by Wilder and his associates,¹⁸ and the potassium content of foods and the technic of preparing diets of known content of potassium have been reported by Sister Mary Victor.¹⁹ Patients who had Addison's disease received a diet low in potassium (1.6 Gm.) and high in sodium (7.3 Gm.). They reacted unfavorably to an increase in the daily intake of potassium to the amount present in the usual unselected diet (4 Gm.). This sensitivity to potassium in the diet appeared to be more noticeable among patients who were depleted of sodium²⁰ and was less marked when sodium saturation had been accomplished by previous administration of sodium chloride. The mechanism by which potassium produces this effect is still unknown. It cannot be accounted for merely by diuresis or by the excessive excretion of sodium that sometimes follows administration of potassium salts to an edematous patient.

Efforts have been made to attribute the muscular weakness which characterizes adrenal cortical insufficiency to the increased concentration of potassium in the serum.²¹ The explanation does not seem tenable,

15. Allers, W. D.; Nilson, H. W., and Kendall, E. C.: Studies on Adrenalectomized Dogs: The Toxic Action of Potassium, *Proc. Staff Meet., Mayo Clin.* **11**:283-288 (April 29) 1936. Allers, W. D., and Kendall, E. C.: Maintenance of Adrenalectomized Dogs Without Cortin, Through Control of the Mineral Constituents of the Diet, *Am. J. Physiol.* **118**:87-94 (Jan.) 1937. Nilson, H. W.: Corticoadrenal Insufficiency: Metabolism Studies on Potassium, Sodium, and Chloride, *ibid.* **118**:620-631 (March) 1937.

16. (a) Zwemer, R. L., and Truszkowski, R.: The Importance of Cortico-adrenal Regulation of Potassium Metabolism, *Endocrinology* **21**:40-49 (Jan.) 1937. (b) Cleghorn, R. A., and McVicar, G. A.: High Potassium Diet and the Survival of Adrenalectomized Rats, *Nature, London* **138**:124 (July 18) 1936. (c) Harrison and Darrow.¹⁴

17. Harrop and others.^{10a} Swingle and others.¹¹

18. Wilder, R. M.; Kendall, E. C.; Snell, A. M.; Kepler, E. J.; Rynearson, E. H., and Adams, M.: Intake of Potassium, Important Consideration in Addison's Disease, *Arch. Int. Med.* **59**:367-393 (March) 1937.

19. Victor, Sister Mary: A Diet Restricted in Potassium, *J. Am. Dietet. A.* **14**:759-772 (Dec.) 1938.

20. Greene, J. A., and Johnston, G. W.: Electrolyte Balance During Treatment, Crises, and Severe Infection in Cases of Addison's Disease, *Arch. Int. Med.* **66**:1052-1059 (Nov.) 1940.

21. Footnote 16 *a* and *b*.

however, since in other conditions, such as some types of nephritis,²² elevation in the concentration of potassium is not necessarily associated with profound weakness. Recently, Miller and Darrow observed that artificially produced increases or decreases in the concentration of potassium in the serum of normal rats have no effect on either voluntary²³ or involuntary²⁴ contraction of muscle.

In a recent review, Fenn²⁵ emphasized present day ignorance of the physiology of potassium. It appears that this ion is intimately related to many physiologic processes which are incompletely understood.

Renal Function.—The abnormal function of the kidney in cases both of experimental adrenal insufficiency and of Addison's disease has received some study. This subject is of fundamental importance because it bears directly on one of the unsolved problems of adrenal cortical function, namely, the site of action of adrenal cortical substances. The question arises whether such substances exert their influence primarily and specifically on the cells of the kidney or whether they affect the behavior of most, if not all, the cells in the organism. If the latter is true, the distinctive type of renal insufficiency which accompanies Addison's disease would represent only the renal aspects of profound changes taking place within the cells of the body as a whole.

Harrison and Darrow²⁶ attacked this problem by measuring the ability of the kidneys of adrenalectomized animals to remove sodium and potassium from the blood stream. They demonstrated that clearance of sodium was increased and clearance of potassium decreased in adrenalectomized animals after treatment with adrenal cortical extract was discontinued. Resumption of specific treatment restored the values for these clearances to normal. They concluded that marked disturbance in renal function of a specific type occurred after adrenalectomy and stated: ". . . the primary change is a failure of the renal tubules to maintain the necessary concentration differences between urine and plasma with respect to certain ions."

22. The observations of Rabinowitch, Nelken and Steinitz and Bolliger and Breh were cited by Harrison and Darrow.¹⁴

23. Miller, H. C., and Darrow, D. C.: Relation of Serum and Muscle Electrolyte, Particularly Potassium, to Voluntary Exercise, *Am. J. Physiol.* **132**:801-809 (April) 1941.

24. Miller, H. C., and Darrow, D. C.: The Effect of Changes in Muscle Electrolyte on the Response of Skeletal Muscle to Tetanic Stimulation with Particular Reference to Potassium, *Am. J. Physiol.* **129**:264-270 (May) 1940.

25. Fenn, W. O.: The Role of Potassium in Physiologic Processes, *Physiol. Rev.* **20**:377-415 (July) 1940.

26. Harrison, H. E., and Darrow, D. C.: Renal Function in Experimental Adrenal Insufficiency, *Am. J. Physiol.* **125**:631-643 (April) 1939.

There is some evidence, according to Willson and Sunderman,²⁷ to indicate that although the kidneys of patients who have Addison's disease ordinarily secrete too much sodium chloride, under certain conditions they cannot secrete enough. For example, a large amount of sodium chloride (15 Gm. in addition to that contained in the diet) and small amounts of water (600 cc. daily) were administered to patients who had Addison's disease; the maximal concentrations of sodium and chloride in the urine were significantly less than those in the urine of normal persons treated in this manner. Because of this limited power to concentrate sodium in the urine, a definite positive balance for sodium and chloride developed in 2 patients who had Addison's disease, whereas it did not develop in persons without the disease. Furthermore, during this period when the maximal concentrations of sodium and chloride were being maintained, the kidneys secreted a relatively large volume of urine in comparison with the amount of water ingested. Such a negative water balance in cases of Addison's disease maintained for any length of time results in the clinical picture of crisis in spite of the fact that the body is, figuratively speaking, pretty well saturated with sodium chloride. This observation lends support to the idea that renal function is severely deranged in the presence of Addison's disease.

The largely functional character of this renal disorder, however, is suggested by the fact that it is not permanent and can be corrected for the most part by administration of adrenal cortical compounds.²⁸ The absence of significant histologic changes in the kidneys in cases of fatal adrenal insufficiency further supports the view.²⁸

In addition, acute adrenal insufficiency is associated with secondary disturbances in renal function²⁹ which are similar to those observed in cases of dehydration or shock from any cause and which are sometimes referred to under the term extrarenal azotemia. In the case of acute adrenal insufficiency these disturbances appear to result largely from diminished glomerular filtration and manifest themselves in part by diminished clearance and by retention of urea and potassium.

Changes in the Body Fluids in Addison's Disease.—The crisis of Addison's disease is characterized by a shocklike state which is asso-

27. Willson, D. M., and Sunderman, F. W.: Studies in Serum Electrolytes: XII. The Effect of Water Restriction in a Patient with Addison's Disease Receiving Sodium Chloride, *J. Clin. Investigation* **18**:35-43 (Jan.) 1939. Willson, D. M.: Electrolyte Balance Studies in Addison's Disease, Thesis, University of Minnesota Graduate School of Medicine, 1940.

28. Gersh, I., and Grollman, A.: Kidney Function in Adrenal Cortical Insufficiency, *Am. J. Physiol.* **125**:66-74 (Jan.) 1939.

29. Smith, H. W.: Kidney, in Luck, J. M., and Hall, V. E.: *Annual Review of Physiology*, Stanford University, Calif., Stanford University Press, 1939, vol. 1, pp. 505-529.

ciated with a decrease in the volume of circulating blood.³⁰ There is considerable evidence that the volume of interstitial fluid³¹ is likewise reduced. Several factors appear to operate in the production of these changes.

One of these factors is the urinary loss of fluid which occurs at the onset of a crisis of adrenal insufficiency.³⁰ This loss, coupled with the usually associated condition of anorexia and diminished ingestion of fluid, results in a negative balance of water. Although frequently encountered, this negative water balance does not appear to be essential in the production of shock in Addison's disease. Harrop and associates,¹³ for example, demonstrated that in experimental animals hemoconcentration and shock will still occur even though a negative water balance is prevented by forced ingestion of water. This occurrence of shock without actual loss of fluid from the animal suggests that in the crisis of Addison's disease a redistribution of water from one compartment of the body to another may occur. Such a redistribution might readily reduce the blood volume and thereby become fully as important as the loss of a large amount of water from the body by diuresis. This conception is sufficiently important to justify its discussion in some detail.

A visual representation of the body fluids and the channels by which their volume can be changed has been prepared by Gamble³² (fig. 1). As may be seen, Gamble visualized the fluids of the body in two main compartments. The fluid in the first, or extracellular, compartment comprises about 20 per cent of the weight of the body and consists of the plasma and the interstitial fluid, which is essentially a protein-free dialysate of the plasma. This fluid represents the *milieu intérieur* of Claude Bernard and functions primarily in the transportation of materials to and from the cells. The fluid in the second major compartment consists of that within the cells. The volume of this compartment is larger, and its contents make up approximately 50 per cent of the body weight.

It is generally realized that the volume of plasma remains relatively constant, even though the intake of fluid varies considerably. This constancy is maintained at the expense of the interstitial fluid, which acts

30. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: Studies on the Suprarenal Cortex: II. Metabolism, Circulation, and Blood Concentration During Suprarenal Insufficiency in the Dog, *J. Exper. Med.* **58**:1-16 (July) 1933. Swingle, W. W.; Vars, H. M., and Parkins, W. M.: A Study of the Blood Volume of Adrenalectomized Dogs, *Am. J. Physiol.* **109**:488-501 (Sept.) 1934.

31. Harrop, G. A.: The Influence of the Adrenal Cortex upon the Distribution of Body Water, *Bull. Johns Hopkins Hosp.* **59**:11-24 (July) 1936.

32. Gamble, J. L.: Extracellular Fluid and Its Vicissitudes, *Bull. Johns Hopkins Hosp.* **61**:151-173 (Sept.) 1937.

as a large reservoir adding fluid to or removing it from the blood stream as circumstances require. Secondary changes in blood volume occur only when this reservoir is seriously overfilled or depleted.

The migration of water back and forth from the cell to the extra-cellular space appears to be determined mainly by differences in osmotic pressure on the two sides of the cell membrane. Although the chemical composition of the fluid within the cell is different from that of the extra-cellular fluid (fig. 2), the osmotic pressures on the two sides of the cell

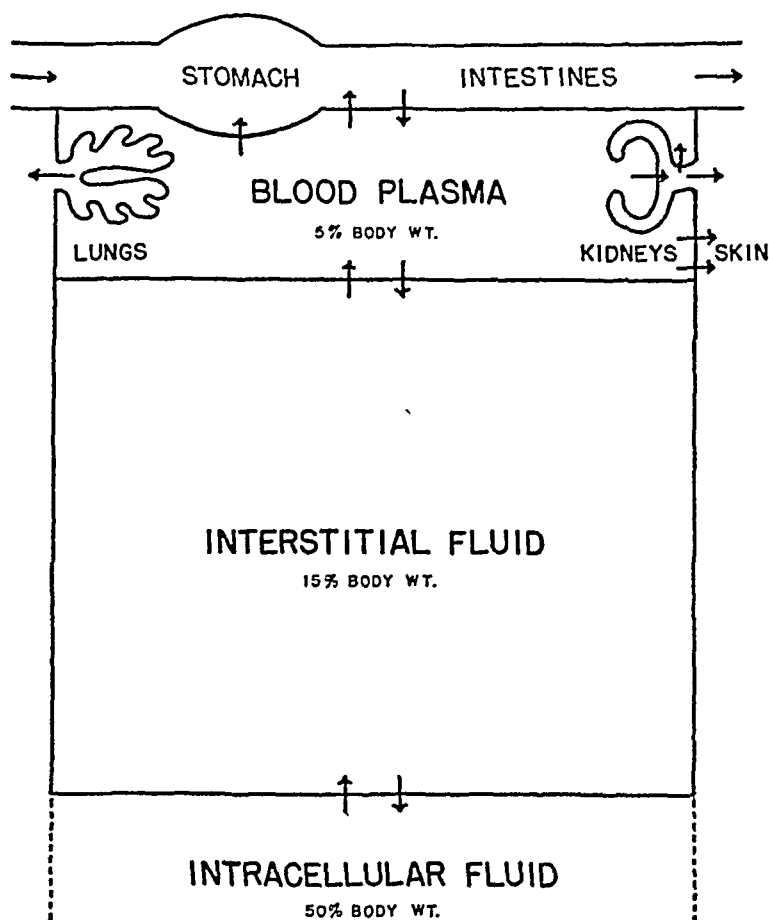


Fig. 1.—The approximate distribution of fluids in the various compartments of the body (Gamble³²).

membrane remain essentially equal. For practical purposes the osmotic pressure of the interstitial fluid is determined largely by its concentration of sodium.³³

33. Since more than 90 per cent of extracellular base is sodium, changes in the remaining basic ions have little effect on the concentration of total bases. The acid ions, chloride, bicarbonate and protein, play only a secondary role in the body economy; their total ionic concentration is automatically regulated by respiration and by the kidneys to equal the total concentration of base. For a detailed discussion of this phase of the problem, the reader is referred to the admirable exposition by Gamble.³²

These basic concepts may be applied to the pathologic physiology of Addison's disease. As adrenal cortical insufficiency increases the following sequence of events may occur: Initially there is a loss of sodium from the body by way of the urine. This loss progresses, and the interstitial fluid becomes more or less depleted of sodium. The osmotic pressure of the interstitial fluid, therefore, decreases relative to that of the cell. To maintain osmotic equilibrium, interstitial water

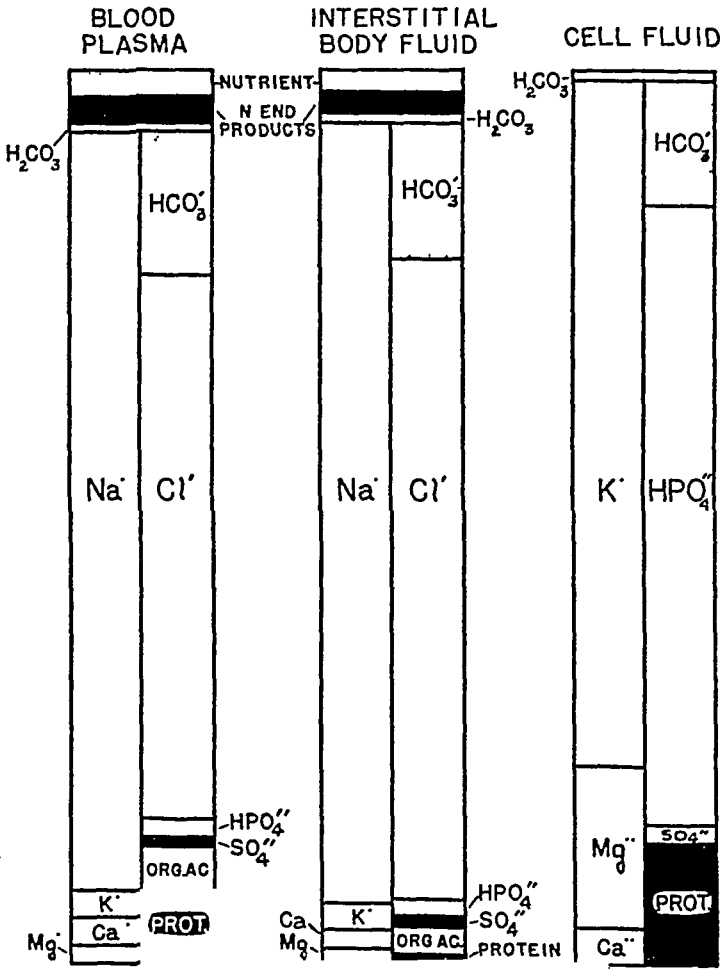


Fig. 2—The approximate distribution of electrolytes in the various body fluids (Gamble ³²).

migrates into the cell. (The cell membrane [thought to be semipermeable] prevents equalization of osmotic pressure by a movement of electrolytes from the cell into the interstitial fluid.) As a result of this movement of water into the cell the cellular fluid is diluted and the interstitial fluid is concentrated. Osmotic pressures on the two sides of the cell membrane are thereby equalized at the expense of a decreased volume of interstitial fluid. Loss of salt and water continues to occur

by way of the urine, the volume of interstitial fluid continues to decrease and finally the volume of blood itself is diminished.

Although this concept of adrenal cortical insufficiency admittedly is hypothetical, it does have the backing of some experimental evidence. Harrison and Darrow,¹⁴ for example, analyzed muscles obtained from adrenalectomized and from normal animals all of which had been depleted of sodium. They demonstrated that as the concentration of sodium in the extracellular fluid decreased the water content of the cells increased, indicating that water had migrated into the cells. Similar results have been obtained by other workers.³⁴

In the evaluation of this concept of adrenal cortical insufficiency and the experimental evidence on which it is based, the limitations of methods for analyzing and measuring the volume of intracellular and extracellular fluids must be remembered. The technics employed are difficult, and the methods yield results which are essentially inferential. In spite of these limitations, the deductions which have been made are worth serious consideration.

The diagram taken from an article by Darrow and Yannet³⁵ will aid those who have not been particularly interested in this problem (fig. 3). This diagram represents an animal weighing 10 Kg. Under normal conditions, the fluid in the extracellular compartments will amount to 2 liters and the fluid within the cells to 5 liters. Darrow and Yannet stated that the concentration of electrolytes, and hence the osmotic pressure, is normally a little higher within the cells than it is in the fluid in the surrounding interstitial space. On the removal of 100 milliequivalents of electrolytes (such as 5.85 Gm. of sodium chloride) from the extracellular fluid there will be a decrease in the osmotic pressure of the extracellular fluid. To compensate for this, fluid will migrate into the cells, diluting the intracellular fluid and reestablishing osmotic equilibrium. In the instance cited this will lead to a 25 per cent reduction in the volume of extracellular fluid and a corresponding increase in the fluid within the cells. Such a change can result in shock. This type of dehydration is essentially little different in its effect on the volume of blood from the dehydration associated with the direct loss of fluid from

34. Hegnauer, A. H., and Robinson, E. J.: The Water and Electrolyte Distribution Among Plasma, Red Blood Cells, and Muscle After Adrenalectomy, *J. Biol. Chem.* **116**:769-778 (Dec.) 1936. Muntwyler, E.; Mautz, F. R.; Mangun, G., and Mellors, R. C.: Electrolyte and Water Exchanges Between Muscle and Blood in Adrenal Insufficiency, *ibid.* **128**:lxxiv (June) 1939. Yannet, H., and Darrow, D. C.: The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle, Liver, and Cardiac Muscle, *ibid.* **134**:721-737 (July) 1940.

35. Darrow, D. C., and Yannet, H.: The Changes in the Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, *J. Clin. Investigation* **14**:266-275 (March) 1935.

the body, as by hemorrhage. In this instance, however, the fluid has not actually been lost; it has migrated into the cells, where it is immobilized.

The converse of this phenomenon is readily apparent. The addition of electrolytes to the extracellular compartment (clinically observed in the retention of sodium which occurs with the administration of desoxycorticosterone) will result in an increase in the osmotic pressure of the extracellular fluid and the migration of fluid from the cells into the interstitial spaces. If these changes are carried to an extreme, hydremia, or increase in the volume of circulating blood, will occur.

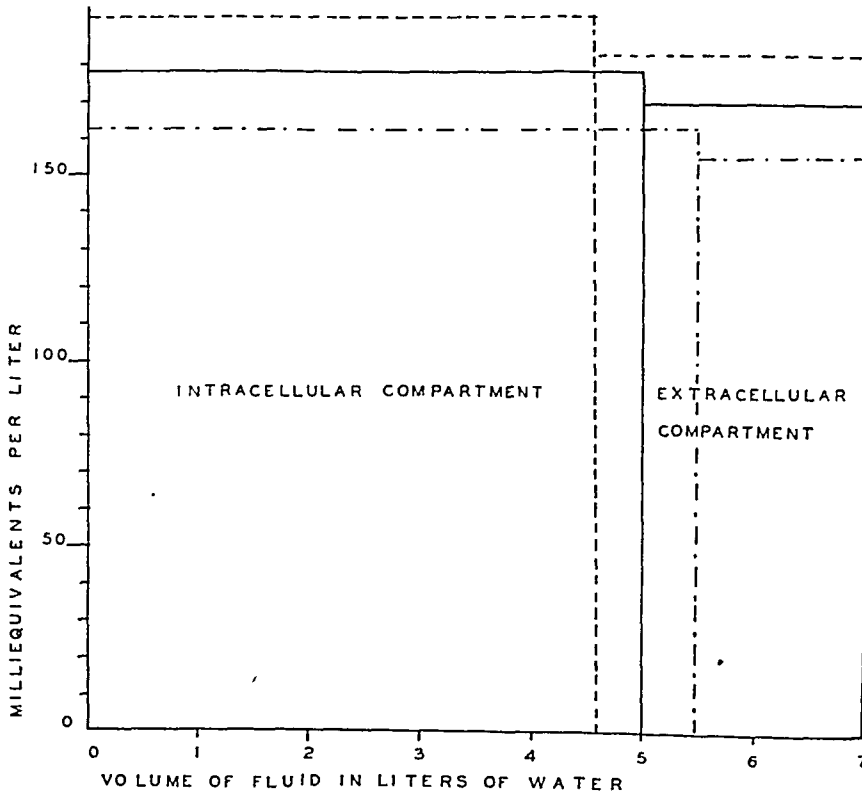


Fig. 3.—A diagrammatic representation of the distribution of body water and electrolytes. The areas bounded by the lines representing volume and concentration indicate the total amount of intracellular or extracellular electrolyte. The solid lines give the distribution under normal conditions; the lines made up of dots and dashes indicate the distribution after the removal of 100 milliequivalents of extracellular electrolyte; the lines made up of dashes represent the distribution after the addition of 100 milliequivalents of extracellular electrolyte (Darrow and Yannet³⁵).

Extrarenal Physiology.—The preceding observations concerning the metabolism of water and electrolytes in adrenal insufficiency have dealt primarily with the results of a disordered function of the kidney. It would be incorrect to assume from this, however, that the kidney is the

sole site of the disorder. Observations made on adrenalectomized rats³⁶ from which the kidneys were removed refute such a hypothesis. It has been demonstrated that such animals do not survive as long as animals which have been merely nephrectomized. Furthermore, the administration of an extract of the adrenal cortex will prolong the survival time and minimize the increase in the concentration of potassium in the plasma of animals from which both the kidneys and the adrenal glands have been removed.

Similarly, Swingle and his associates³⁷ observed that when adrenal cortical extract was withheld from an adrenalectomized dog the classic symptoms and signs of crisis developed despite the fact that the animal had anuria and thus could not have lost sodium in the urine. These workers³⁸ also observed that dogs can recover from crisis after administration of large amounts of cortical extract in a period when sodium chloride is not administered and there is no change in the concentration of sodium in the serum.

These and numerous other observations suggest that the adrenal cortex exerts an influence on the organism which is entirely independent of its effect on the kidney. The nature of this influence is incompletely understood at present, however, and the elucidation of this problem is complicated by the technical difficulties which beset investigators of cellular physiology.

Carbohydrate Metabolism.—Evidence which has accumulated for some years indicates that carbohydrate metabolism is influenced by the adrenal cortex. Britton and Silvette³⁹ were early proponents of this idea. They demonstrated that when the adrenal glands were removed

36. Ingle, D. J., and Kendall, E. C.: Survival of the Adrenalectomized Nephrectomized Rat, *Am. J. Physiol.* **117**:200-202 (Oct.) 1936. Ingle, D. J.; Nilson, H. W., and Kendall, E. C.: The Effect of Cortin on the Concentration of Some Constituents of the Blood of Adrenalectomized Rats, *ibid.* **118**:302-308 (Feb.) 1937. MacKay, E. M.; Bergman, H. C., and MacKay, L. L. L.: Serum Potassium and Sodium as Altered by Adrenalectomy and Nephrectomy, *ibid.* **120**:83-86 (Sept.) 1937. Hartman, F. A., and Dubach, R.: The Effect of Adrenal Preparations on the Adrenalectomized-Nephrectomized Rat, *Endocrinology* **27**:638-641 (Oct.) 1940.

37. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: The Influence of Adrenal Cortical Hormone upon Electrolyte and Fluid Distribution in Adrenalectomized Dogs Maintained on a Sodium and Chloride Free Diet, *Am. J. Physiol.* **119**:684-691 (Aug.) 1937.

38. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: Relation of Serum Sodium and Chloride Levels to Alterations of Body Water in the Intact and Adrenalectomized Dog, and the Influence of Adrenal Cortical Hormone upon Fluid Distribution, *Am. J. Physiol.* **116**:438-445 (July) 1936.

39. Britton, S. W., and Silvette, H.: The Apparent Prepotent Function of the Adrenal Glands, *Am. J. Physiol.* **100**:701-713 (May) 1932.

from the guinea pig, cat and other species hypoglycemic convulsive seizures occurred. In addition, it was found that supplies of glycogen in the liver and muscles of such animals were reduced and that the ability to form hepatic glycogen from injections of dextrose or sodium lactate was diminished.

For a long time the importance of these disturbances of carbohydrate metabolism which occurred after adrenalectomy were overshadowed by the seemingly more important alterations in electrolyte metabolism. Furthermore, the results of the studies of this subject frequently were conflicting or inconclusive. In fact, some writers expressed the opinion that the changes in carbohydrate metabolism which had been encountered were entirely nonspecific phenomena secondary to the malnutrition usually present.

Long, Katzin and Fry⁴⁰ reviewed this earlier work and disclosed the reasons for some of the discrepancies in results which had been encountered. For example, they pointed out that different species of animals behave differently after adrenalectomy in respect to the duration of survival and the rapidity with which changes in electrolyte and/or carbohydrate metabolism ensue. In some species fatal alterations in electrolyte metabolism occur so rapidly that changes in carbohydrate metabolism do not become apparent; in others the animal survives long enough to permit marked alterations in the level of blood sugar and the content of hepatic and muscle glycogen to take place. These authors also called attention to the necessity of controlling the intake of food prior to analyzing tissues for glycogen. Some animals refuse food after adrenalectomy; others eat until just before death. Under such circumstances, it is not surprising that discrepant results have been obtained by different workers.

In spite of the difficulties which arise in conducting decisive experiments, it now has been shown, at least in certain species, that carbohydrate metabolism unquestionably is deranged by removal of the adrenal cortex. A summary of some of the various observations follows.

Fasting: Adrenalectomized rats⁴⁰ or mice can be maintained in good health for a long time by judicious administration of sodium salts. As long as the animals are fed, normal levels of glycogen in the liver and muscle and of sugar in the blood are maintained. However, fasting adrenalectomized animals lose hepatic glycogen rapidly, ultimately lose glycogen from the muscles and finally, at the end of forty-eight hours, become hypoglycemic and often have convulsions. These changes can be prevented by the administration of adrenal cortical extract. Further-

40. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, *Endocrinology* **26**:309-344 (Feb.) 1940.

more, administration of this substance to adrenalectomized rats receiving a normal diet results in a striking increase in the deposition of glycogen in the liver.⁴¹

Comparable observations were made by Thorn and associates⁴² in a case of Addison's disease. The appearance of hypoglycemia in this instance seemed to be related to lack of carbohydrate. Thus, although the patient received a daily diet of average caloric content but composed of large amounts of fat and deficient in carbohydrate, hypoglycemia, in which the value for blood sugar was 55 mg. per hundred cubic centimeters, developed within sixty hours. The symptoms were sufficiently severe to necessitate the intravenous administration of dextrose.

Phlorhizin Diabetes and Gluconeogenesis: As is well known, administration of phlorhizin lowers the renal threshold for dextrose, so that sugar is constantly excreted in the urine as long as the endogenous and exogenous supplies hold out. Since the supply of glycogen available for the formation of dextrose in the fasting animal is limited, it must be concluded that the continued excretion of dextrose is maintained at the expense of protein, the chief endogenous source. Fasting adrenalectomized rats and dogs maintained in health by the administration of sodium chloride alone excrete considerably less sugar after administration of phlorhizin than do normal control animals.⁴³ This defect can be corrected by the administration of certain crystalline compounds obtained from the adrenal cortex (fully by corticosterone and compound E [17-hydroxy-11-dehydrocorticosterone] but only partially by desoxycorticosterone).⁴⁴ This work indicates that in adrenalectomized animals the endogenous supply of dextrose, namely protein, either is deficient in amount or is relatively immobile.

Further studies⁴⁵ suggested that the latter of these two possibilities is the more likely and that adrenalectomy in a sense immobilizes protein, so that the rate at which it is converted into dextrose is retarded. Stated somewhat differently, the rate of protein catabolism is diminished.

41. Sprague, R. G.: The Influence of Extract of the Adrenal Cortex on Glycogenesis in Fasting Rats, *Proc. Staff Meet., Mayo Clin.* **15**:291-294 (May 8) 1940.

42. Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, *J. Clin. Investigation* **19**:813-832 (Nov.) 1940.

43. (a) Evans, G.: The Adrenal Cortex and Endogenous Carbohydrate Formation, *Am. J. Physiol.* **114**:297-308 (Jan.) 1936. (b) Lewis, R. A.; Kuhlman, D.; Delbue, C.; Koepf, G. F., and Thorn, G. W.: The Effect of the Adrenal Cortex on Carbohydrate Metabolism, *Endocrinology* **27**:971-982 (Dec.) 1940.

44. Wells, B. B.: The Influence of Crystalline Compounds Separated from the Adrenal Cortex on Gluconeogenesis, *Proc. Staff Meet., Mayo Clin.* **15**:294-297 (May 8) 1940.

45. Long, Katzin and Fry.⁴⁰ Lewis and others.^{43b} Wells.⁴⁴

If this were true, it would be expected that adrenalectomy would reduce the amount of nitrogen excreted in the urine. It also would be expected that the dextrose-nitrogen ratio in cases of phlorhizin diabetes would be little affected by adrenalectomy, since both the dextrose and the nitrogen excreted in the urine would be diminished proportionately. Actually, most of these theoretic expectations were observed to be fulfilled in fasting adrenalectomized rats. Divergent results regarding the dextrose-nitrogen ratio have been obtained, however, by some workers.

Although adrenalectomy appears to interfere with the formation of dextrose (and glycogen) from endogenous protein, it appears to have no effect on the metabolism of exogenous protein. Wells and Kendall,⁴⁶ for example, have stated:

Adrenalectomized phlorhizinized rats, when given casein alone, were able to metabolize this protein, excrete the expected amounts of glucose and nitrogen and in every way respond as normal phlorhizinized rats without treatment with any hormone from the adrenal gland. It seems evident that the metabolism of exogenous protein is not seriously disturbed by the absence of the adrenal cortical hormones.

Experimental Diabetes: That adrenalectomy reduces the amount of sugar which appears in the urine of totally depancreatized animals has been known for some time. Long, Katzin and Fry⁴⁰ investigated this phenomenon further and found that it also occurred if the animal (rat) was only partially depancreatized. They also demonstrated that administration of adrenal cortical extract caused a return of sugar in the urine to the level that was present before the adrenal glands were removed. In fact, if sufficient amounts of adrenal cortical extract were administered, the degree of glycosuria which ensued actually was greater than that which was present before adrenalectomy. Furthermore, these authors noted that adrenal cortical extract intensified the excretion of sugar in partially depancreatized rats that had intact adrenal cortices.

Sprague,⁴¹ in confirming these observations, demonstrated that the administration of adrenal cortical extract to partially depancreatized rats was followed by an increased amount of glycogen in the liver, even though the animals were fasting. From these observations it would appear that although adrenal cortical extracts have the capacity of intensifying one aspect (namely, glycosuria) of experimental diabetes in rats, they also tend, by causing increased storage of glycogen, to ameliorate another.

Insulin: Considerable difference has been observed in the responses of normal and of adrenalectomized animals to intravenous injection of small amounts of insulin. Lewis^{43b} and his associates disclosed that

46. Wells, B. B., and Kendall, E. C.: The Influence of the Adrenal Cortex on Phlorhizin Diabetes, *Proc. Staff Meet., Mayo Clin.* **15**:565-573 (Sept. 4) 1940.

normal dogs tolerated 0.25 unit of insulin per kilogram of body weight, whereas the same amount of insulin caused hypoglycemia and severe convulsions in adrenalectomized dogs. If large doses of adrenal cortical extract were administered to adrenalectomized dogs in the course of the twelve hours before the injection of insulin, hypoglycemia was less pronounced. Furthermore, it was demonstrated that insulin caused convulsions in adrenalectomized dogs before the concentration of blood sugar was reduced to the low level usually associated with symptoms of hypoglycemia. Treatment with cortical extract prevented these convulsions from occurring until the concentration of the blood sugar was at the level at which such convulsions ordinarily are expected.

Standard Dextrose Tolerance Tests: Thorn and his associates⁴² demonstrated that patients who have Addison's disease tend to have a flat type of curve in response to the dextrose tolerance test when the sugar is given orally. This phenomenon, according to Thorn, appears to be the result of slow absorption of dextrose from the intestinal tract, a condition similar to that observed in cases of sprue. When dextrose was given intravenously the results in cases of Addison's disease did not differ significantly from the results in control cases except that in the former symptoms of hypoglycemia occurred more frequently in the third hour. The symptoms of hypoglycemia, which were often exceedingly severe, frequently occurred when the concentration of sugar in the blood was only moderately reduced. Spontaneous recovery was unusual. Treatment with adrenal cortical extract increased the fasting level of sugar in the blood, restored the dextrose tolerance curve to normal and prevented signs and symptoms of hypoglycemia. Similar changes with regard to the response to the dextrose tolerance test have been observed in adrenalectomized dogs.⁴⁷

Intermediary Carbohydrate Metabolism: Suggestions based on some evidence have been advanced that adrenal cortical insufficiency is associated with a disturbance in the intermediate metabolism of carbohydrate. Reference⁴⁸ already has been made to the diminished stores of glycogen in the livers of adrenalectomized animals. Britton and Silvette⁴⁹ were unable to correct this depletion of glycogen in adrenalectomized cats by intraperitoneal injection of sodium lactate. Subsequently similar results

47. Kendall, E. C.; Flock, E. V.; Bollman, J. L., and Mann, F. C.: The Influence of Cortin and Sodium Chloride in Carbohydrate and Mineral Metabolism in Adrenalectomized Dogs, *J. Biol. Chem.* **126**:697-708 (Dec.) 1938. Lewis and others.^{43b}

48. Britton and Silvette.³⁹ Long, Katzin and Fry.⁴⁰ Sprague.⁴¹

49. Britton, S. W., and Silvette, H.: On the Function of the Adrenal Cortex—General, Carbohydrate and Circulatory Theories, *Am. J. Physiol.* **107**:190-206 (Jan.) 1934.

were obtained for rats.⁵⁰ Similarly, the intravenous administration of racemic sodium lactate failed to relieve the hypoglycemic symptoms of adrenalectomized dogs^{43b} and of a patient who had Addison's disease.⁴² Diminished ability of adrenalectomized animals^{43b} to convert lactic acid, pyruvic acid or the amino acid alanine (alphaaminopropionic acid) into dextrose has been observed in adrenalectomized, phlorhizinized rats. Failure to obtain the calculated amounts of dextrose in the urine after the administration of these potentially glycogenic substances is interpreted as a failure of formation of dextrose from these precursors.

Disturbances of Carbohydrate Metabolism in Cases of Addison's Disease: In contrast to observations on experimental animals, striking abnormalities of carbohydrate metabolism are rarely encountered in cases of Addison's disease. Anderson and Lyall⁵¹ reported 1 case of atrophy of the adrenal glands in which fatal hypoglycemia occurred. They mentioned 2 instances of a similar episode recorded in the literature. Rushton and his associates⁵² recently reported similar observations in another case of primary atrophy of the adrenal glands and were able to find an additional case in the literature. The occurrence in the literature of these few cases confirms the clinical impression that hypoglycemia is not a prominent feature of this condition. The fact cannot be ignored, however, that occasionally hypoglycemia with symptoms does occur in cases of Addison's disease.

Summary.—Enough evidence has been outlined to justify the original contention of Britton and Silvette⁴⁹ that in certain species of animals adrenal cortical insufficiency is associated with serious derangement of the metabolism of carbohydrate. This derangement has a definite pattern, characterized largely by (1) decreased rate of formation of dextrose from endogenous protein; (2) impaired synthesis of dextrose from a common precursor, such as lactic acid; (3) diminished supplies of glycogen in the liver and muscles, and (4) increased sensitivity to insulin. These disturbances vary among different species of animals. They can be corrected by injections of cortical extract or of some of the crystalline compounds which have been isolated from this extract.

How are these various abnormalities produced? What is their relation to the metabolism of "salt and water"? Why do they resemble

50. Buell, M. V.; Anderson, I. A., and Strauss, M. B.: On Carbohydrate Metabolism in Adrenalectomized Animals, *Am. J. Physiol.* **116**:274-281 (July) 1936.

51. Anderson, I. A., and Lyall, A.: Addison's Disease Due to Suprarenal Atrophy with Previous Thyrotoxicosis and Death from Hypoglycemia, *Lancet* **1**: 1039-1043 (May 1) 1937.

52. Rushton, J. G.; Cragg, R. W., and Stalker, L. K.: Spontaneous Hypoglycemia Due to Atrophy of the Adrenal Glands, *Arch. Int. Med.* **66**:531-540 (Sept.) 1940.

so closely the disturbances produced by removal of the anterior lobe of the hypophysis? At present one can only conjecture. For a more comprehensive treatment of this phase of the problem, the reader is referred to the excellent reviews⁵³ which have appeared recently.

ADRENAL CORTICAL SUBSTANCES

In the previous review,¹ mention was made of adrenal cortical extracts prepared by Rogoff and Stewart, by Hartman and his collaborators and by Swingle and Pfiffner, which were capable of supporting life in adrenalectomized animals. Since that time methods of preparation have improved. At present, potent extracts can be obtained from several pharmaceutical houses.⁵⁴ One of the great difficulties encountered in the preparation and standardization of these extracts has been the lack of suitable methods of assay. Numerous procedures, based on growth,⁵⁵ survival time,⁵⁶ prevention of muscular fatigue⁵⁷ and maintenance of normal concentrations of urea, electrolytes⁵⁸ and so forth in the blood,⁵⁹ have been advocated. Different methods of assay which test different physiologic activities often yield conflicting results, and as yet there is no unanimity of opinion as to which of these various procedures is most suitable.

Remarkable progress has been made in the isolation and identification of crystalline (steroid) compounds obtained from the adrenal cortex. Investigations have been carried on primarily by three groups

53. Soskin, S.: Metabolic Function of the Endocrine Glands, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1941, vol. 3, pp. 543-572. Kendall, E. C.: The Adrenal Cortex, Arch. Path. **32**:474-501 (Sept.) 1941.

54. Loeb, R. F.: Conferences on Therapy: Treatment of Addison's Disease, J. A. M. A. **112**:2511-2516 (June 17) 1939.

55. Hartman, F. A., and Thorn, G. W.: A Biological Method for the Assay of Cortin, Proc. Soc. Exper. Biol. & Med. **28**:94-95 (Nov.) 1930.

56. Kutz, R. L.: A Method of Assay of Extracts Containing the Suprarenal Cortical Hormone, Proc. Soc. Exper. Biol. & Med. **29**:91-93 (Oct.) 1931.

57. Ingle, D. J.: Work Capacity of the Adrenalectomized Rat Treated with Cortin, Am. J. Physiol. **116**:622-625 (Aug.) 1936.

58. Harrop, G. A.; Pfiffner, J. J.; Weinstein, A., and Swingle, W. W.: A Biological Method of Assay of the Adrenal Cortical Hormone, Proc. Soc. Exper. Biol. & Med. **29**:449-451 (Jan.) 1932.

59. Pfiffner, J. J.; Swingle, W. W., and Vars, H. M.: The Cortical Hormone Requirement of the Adrenalectomized Dog, with Special Reference to a Method of Assay, J. Biol. Chem. **104**:701-716 (March) 1934. Harrop, G. A., and Thorn, G. W.: Studies on the Suprarenal Cortex: VI. The Effect of Suprarenal Cortical Hormone upon the Electrolyte Excretion of the Intact Normal Dog; a Proposed Method of Comparative Assay, J. Exper. Med. **65**:757-766 (June) 1937. Selye, H., and Schenker, V.: A Rapid and Sensitive Method for Bioassay of the Adrenal-cortical Hormone, Proc. Soc. Exper. Biol. & Med. **39**:518-522 (Dec.) 1938.

of workers, namely, Reichstein and his associates, in Zurich, Switzerland; Wintersteiner and Pfiffner, at Columbia University, and Kendall, Mason and associates, at the Mayo Foundation. Although a great many compounds which are closely related in chemical structure to progesterone (fig. 4) have been isolated, only a few appear to have significant physiologic activity.⁶⁰ Furthermore, according to Wells and Kendall,⁶¹ the total activity of the compounds represents only a small fraction of

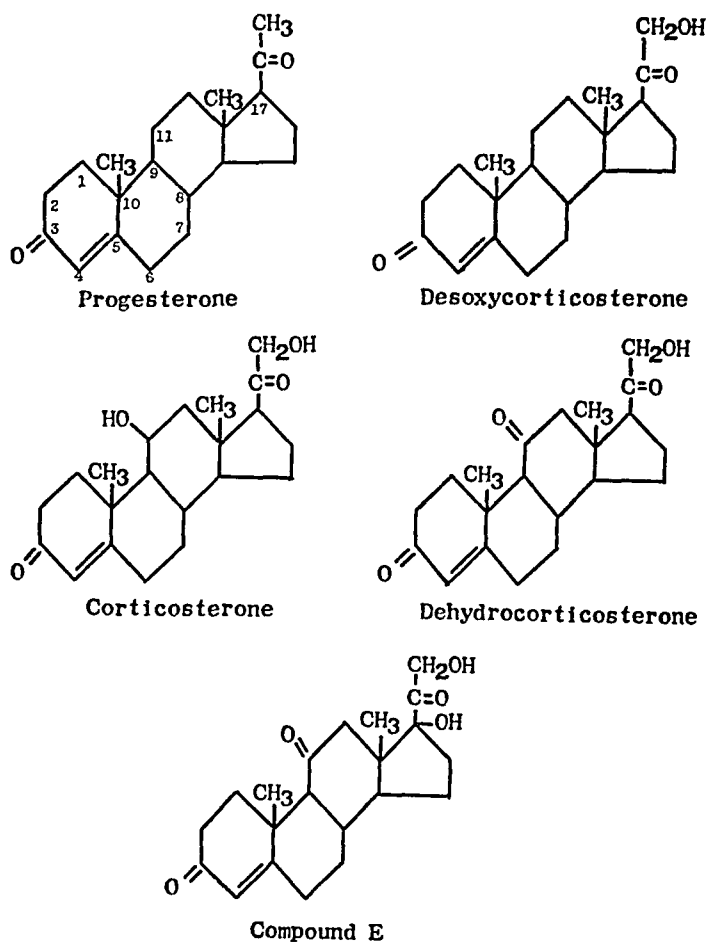


Fig. 4.—The structural similarity of some of the active compounds isolated from the adrenal cortex to progesterone.

the activity of the crude extract. For example, after removal of these crystalline substances from the crude extract, an unidentified amorphous

60. Mason, H. L.: Chemistry of the Adrenal Cortical Hormone, *Endocrinology* **25**:405-412 (Sept.) 1939.

61. Wells, B. B., and Kendall, E. C.: A Qualitative Difference in the Effect of Compounds Separated from the Adrenal Cortex on Distribution of Electrolytes and on Atrophy of the Adrenal and Thymus Glands of Rats, *Proc. Staff Meet., Mayo Clin.* **15**:133-139 (Feb. 28) 1940.

material still remains which retains 90 per cent of the potency of the original material as far as the maintenance of a normal electrolyte pattern in adrenalectomized dogs is concerned.

Desoxycorticosterone.—Clinically, the most important compound is desoxycorticosterone. This substance was first synthesized by Reichstein, who subsequently isolated it from extracts of the adrenal cortex. It is dispensed as desoxycorticosterone acetate dissolved in a vegetable oil and as yet is the only one of the compounds available for clinical use in a synthetic form. This substance causes retention of sodium and chloride and augments the excretion of potassium and phosphorus.⁶² In cases of Addison's disease it increases the volume of plasma, rectifies the abnormal electrolyte pattern of the plasma and raises the blood pressure. After its administration the patient has a sense of well-being and his general condition improves. When large amounts of desoxycorticosterone acetate are administered excessive retention of sodium and chloride occurs, the stores of potassium are depleted and the blood volume increases above normal limits.⁶³ Rarely the concentration of sodium in the plasma remains subnormal, even though the level of potassium in the plasma is reduced. In contrast to this marked effect on electrolyte metabolism, desoxycorticosterone seems to have only a slight effect on carbohydrate metabolism.

Corticosterone, Dehydrocorticosterone and 17-Hydroxy-11-dehydrocorticosterone (Compound E of Kendall; Compound F of Pfiffner and Wintersteiner).—These three compounds isolated from the adrenal

62. (a) Thorn, G. W., and Eisenberg, H.: Studies on Desoxy-Corticosterone, *Endocrinology* **25**:39-46 (July) 1939. (b) Thorn, G. W.; Engel, L. W., and Eisenberg, H.: The Effect of Corticosterone and Related Compounds on the Renal Excretion of Electrolytes, *J. Exper. Med.* **68**:161-172 (Aug.) 1938. (c) Simpson, S. L.: The Use of Desoxycorticosterone Acetate in Addison's Disease, *Lancet* **2**:557 (Sept. 3) 1938. (d) McCullagh, E. P.: Sodium and Chloride Retention in Addison's Disease Treated with Desoxycorticosterone Acetate, *Cleveland Clin. Quart.* **6**:105-108 (April) 1939. (e) Dryerre, H. W.: Effect of Desoxycorticosterone Acetate and Cortin on Salt Elimination in Addison's Disease, *Brit. M. J.* **1**:971-973 (May 13) 1939. (f) Thorn, G. W.; Howard, R. P., and Emerson, K., Jr.: Treatment of Addison's Disease with Desoxy-Corticosterone Acetate, a Synthetic Adrenal Cortical Hormone, *J. Clin. Investigation* **18**:449-467 (July) 1939. (g) Cleghorn, R. A.; Fowler, J. L. A., and Wenzel, J. S.: The Treatment of Addison's Disease by a Synthetic Adrenal Cortical Hormone (Desoxycorticosterone Acetate), *Canad. M. A. J.* **41**:226-231 (Sept.) 1939. (h) Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, *J. A. M. A.* **113**:1725-1731 (Nov. 4) 1939.

63. (a) Willson, D. M.; Rynearson, E. H., and Dry, T. J.: Cardiac Failure Following Treatment of Addison's Disease with Desoxycorticosterone Acetate, *Proc. Staff Meet., Mayo Clin.* **16**:168-173 (March 12) 1941. (b) Ferrebee and others.^{62h}

cortex have in common an oxygen atom attached to carbon atom 11 of the steroid nucleus. In contrast to the action of desoxycorticosterone, they exert a marked effect on carbohydrate metabolism.⁶⁴ After their administration the abnormalities of carbohydrate metabolism associated with experimental adrenal cortical insufficiency appear to be corrected. Glycogen is stored in the liver and hypoglycemia prevented. In addition, compound E (which of all these compounds appears to exert the greatest effect on carbohydrate metabolism) restores the ability of adrenalectomized rats to form dextrose from lactic, pyruvic and glyconic amino acids. In contrast to these results, Hampton,⁶⁵ working with patients who had Addison's disease, was unable to demonstrate any effect of compound E on the hypoglycemic action of insulin.

In addition to their effect on carbohydrate metabolism, these substances exert some effect on the excretion of electrolytes in the adrenalectomized dog. This action is comparatively feeble, however, for 10 mg. of compound E or 2.5 mg. of dehydrocorticosterone is required to produce the same effect on the distribution of electrolytes in the adrenalectomized dog that can be produced by only 0.3 mg. of desoxycorticosterone acetate.⁶⁶

Amorphous Fraction.—This substance is the highly active concentrate of extracts of the adrenal cortex which remains after removal of the crystalline fractions already described. According to Kendall,⁶⁶ it is exceedingly potent in its effects on electrolyte metabolism. Only 1 or 2 micrograms per kilogram of body weight is required to maintain normal electrolyte patterns in the plasma of adrenalectomized dogs. This dose is in decided contrast to the relatively large amount of desoxycorticosterone required to produce the same effect.

It is questioned whether the adrenal cortex elaborates⁶⁷ one substance which can be regarded as the vital hormone of the gland or whether it elaborates a number of hormones, each of which has its own specific effect. A similar question, as yet unanswered, has bedeviled students of the physiology of the anterior portion of the pituitary.

DIAGNOSIS OF ADDISON'S DISEASE

Until comparatively recently, the recognition or exclusion of Addison's disease was based entirely on clinical evidence. In recent years

64. Long, Katzin and Fry.⁴⁰ Wells.⁴⁴ Lewis and others.^{43b} Thorn and others.⁴²

65. Hampton, H. P.: Personal communication to the authors.

66. Kendall, E. C.: Glandular Physiology and Therapy: The Function of the Adrenal Cortex, J. A. M. A. **116**:2394-2398 (May 24) 1941.

67. Kendall, E. C.: The Function of the Adrenal Cortex, Proc. Staff Meet., Mayo Clin. **15**:297-304 (May 8) 1940; Hormones, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1941, vol. 10, pp. 285-336.

several test procedures, however, have been developed which aid considerably in the evaluation of the functional integrity of the adrenal cortex. Among the earliest of these was that suggested by Harrop and associates,⁶⁸ which consisted simply of restricting the dietary intake of sodium chloride. If typical clinical symptoms of addisonian crisis ensued, the patient probably had Addison's disease. This procedure was decidedly hazardous to the patient if he did happen to have Addison's disease. At least 2 deaths have been reported after its use.⁶⁹ It also had the great disadvantage of not giving information that was decisively measurable, and the physician still had to rely largely on his clinical judgment as to what constituted a crisis.

In 1938 Cutler, Power and Wilder⁷⁰ modified and standardized the procedure of Harrop so that the concentration of chlorides in the urine could be utilized for diagnostic purposes. According to their method, the patient receives a standardized quantity of sodium chloride and potassium in the diet. In addition, potassium citrate and water are given in amounts proportional to the body weight. At the end of the fifty-two hours the test is terminated, and the urine voided in the last four hours is analyzed for its concentration of chloride. Under these conditions, patients who have adrenal cortical insufficiency excrete urine in which high concentrations of chloride and sodium are present. A high degree of diagnostic accuracy can be achieved by this method,⁷¹ but the procedure has a number of disadvantages. Considerable time is required; careful chemical determinations are necessary, and it is somewhat haz-

68. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, *J. A. M. A.* **100**:1850-1855 (June 10) 1933.

69. Lilienfield, A.: The Use of the Low Salt Diet in the Diagnosis of Addison's Disease, *J. A. M. A.* **110**:804-805 (March 12) 1938. Garvin, C. F., and Reichle, H. S.: Death Presumably Due to the Use of the Salt Restriction Test in the Diagnosis of Addison's Disease, *Ann. Int. Med.* **14**:323-324 (Aug.) 1940.

70. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Sodium, Chloride, and Potassium in the Blood Plasma and Urine of Patients with Addison's Disease: Their Diagnostic Significance, *Proc. Staff Meet., Mayo Clin.* **13**:244-249 (April 20) 1938; Concentrations of Chloride, Sodium, and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, *J. A. M. A.* **111**:117-122 (July 9) 1938.

71. McCullagh, E. P., and Ryan, E. J.: The Use of Desoxycorticosterone Acetate in Addison's Disease, *J. A. M. A.* **114**:2530-2537 (June 29) 1940. Dryerre, H. W.: Addison's Disease: The Diagnostic Significance of the Sodium and Chloride Content of the Blood and Urine, *Edinburgh M. J.* **46**:267-277 (April) 1939. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease: Clinical Considerations, *J. A. M. A.* **114**:2517-2525 (June 29) 1940. Stephens, D. J.: Pituitary and Adrenocortical Insufficiency: The Use of Sodium Chloride in the Treatment of Hypopituitarism, *J. Clin. Endocrinol.* **1**:109-112 (Feb.) 1941. Thorn, G. W.; Howard, R. P., and Dayman, H.: Electrolyte Changes in Pulmonary Tuberculosis, with Special Reference to Adrenal Cortical Function, *Bull. Johns Hopkins Hosp.* **67**:345-364 (Nov.) 1940.

ardous to the patient who has Addison's disease. In actual practice, in about half of the cases in which the test was performed at the Mayo Clinic it was not possible to complete it because of the occurrence of acute adrenal insufficiency.⁷²

Robinson, Power and one of us (E. J. K.)⁷³ recently developed two closely related procedures which eliminated these difficulties in the majority of instances. The first one is based on a fact not generally appreciated, that after ingestion of large amounts of water patients who have Addison's disease do not experience normal prompt diuresis. This procedure is used primarily to exclude the adrenal cortex as the cause of fatigue states, hypotension, neurasthenia and similar disorders. Since potent adrenal cortical compounds have been made available to members of the medical profession the number of patients with such conditions suspected of having Addison's disease and treated accordingly has greatly increased. Obviously, a simple method of proving that adrenal cortical insufficiency is not the specific cause of the symptoms in these cases is highly desirable. The second procedure continues where the first leaves off. It is essentially chemical in character and is used to establish the diagnosis if the results of the first test indicate that the patient probably has Addison's disease. It has the great advantage of being safe, comparatively simple, rapid and reasonably decisive.

The two tests are conducted in the following manner: The day before the test the patient eats his usual three meals but omits extra salt. After 6 p. m. he does not eat or drink. At 10:30 p. m. he voids and discards the urine. All urine voided from 10:30 p. m. until and including 7:30 a. m. is collected, measured and saved for chemical analysis if this proves to be necessary. At 8:30 a. m. the patient voids again (if possible) and discards the urine. Immediately thereafter he is given 20 cc. of water per kilogram of body weight, or 9 cc. per pound, in the course of forty-five minutes. He is asked to void at 9:30, 10:30 and 11:30 a. m. and 12:30 p. m. Each of the specimens is measured. At 11:30 a. m. or 12:30 p. m. (the exact time is inconsequential) blood is drawn under oil for chemical analysis if the necessity for such studies appears likely, as by this time the results of this first procedure usually will be apparent.

The first procedure is concluded by comparing the volume of urine voided during the night with the volume of the largest single hourly specimen voided between 8:30 a. m. and 12:30 p. m.; the second procedure, by analyzing the urine voided during the night and the blood for

72. Willson, D. M.; Robinson, F. J.; Power, M. H., and Wilder, R. M.: The Diagnosis of Adrenal Cortical Insufficiency: Further Experience with the Cutler-Power-Wilder Salt Restriction Test, *Arch. Int. Med.*, to be published.

73. Robinson, F. J.; Power, M. H., and Kepler, E. J.: Two New Procedures to Assist in the Recognition and Exclusion of Addison's Disease: A Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **16**:577-583 (Sept. 10) 1941.

the concentrations of urea and chloride. A ratio is calculated from the values obtained in these four determinations.

From a study of 90 patients (40 of whom were proved by salt deprivation and by the Cutler, Power and Wilder procedure to have Addison's disease) it was ascertained that if the volume of urine which was voided during the night was less in amount than the volume of urine voided at any one hour during the morning, the patient did not have Addison's disease. If, on the other hand, the volume of urine voided during the night was greater than the volume voided at any one hour during the morning, the patient might or might not have Addison's disease, and the chemical analyses which constitute the second procedure were necessary. Under the latter circumstance the following ratio is calculated from the results of the four chemical determinations:

$$A = \frac{\text{Urea in urine (mg./100 cc.)}}{\text{Urea in plasma (mg./100 cc.)}} \times \frac{\text{Chloride in plasma (mg./100 cc.)}}{\text{Chloride in urine (mg./100 cc.)}} \times \frac{\text{Volume of day urine (cc.)}^{74}}{\text{Volume of night urine (cc.)}}$$

In nearly all instances in which the value for *A* did not exceed 25 the patient was found to have Addison's disease. Values for *A* of more than 30 indicated the absence of Addison's disease. The only exceptions encountered occurred in cases of nephritis. In conjunction with clinical evidence, the procedure proved to be decisively diagnostic in cases in which the presence of Addison's disease was proved by other methods.

Diagnostic methods which depend on the response of patients to specific treatment for Addison's disease have been developed by Thorn and his associates.⁷⁵ To be of value these procedures must be conducted under carefully controlled conditions. The use of mere subjective improvement following specific treatment in the absence of positive chemical data is an unreliable diagnostic criterion. Similarly, the tolerance of patients to the ingestion of potassium has been recommended as a diagnostic aid.⁷⁶ Recent reports,⁷⁷ however, indicate that this method is not wholly reliable.

74. The term "day urine" applies to the largest of the hourly specimens voided during the day and "night urine," to the entire amount which was voided from 10:30 p. m. to 7:30 a. m. It is immaterial how these values are expressed, provided the same unit is used throughout the equation. For example, if the concentration of chloride in the plasma is expressed as milligrams of chloride per hundred cubic centimeters of plasma, the concentration of chloride in the urine should be expressed in the same manner.

75. Thorn, G. W.; Garbutt, H. R.; Hitchcock, F. A., and Hartman, F. A.: The Effect of Cortin on the Sodium, Potassium, Chloride, Inorganic Phosphorus, and Total Nitrogen Balance in Normal Subjects and in Patients with Addison's Disease, *Endocrinology* **21**:202-212 (March) 1937.

76. Zwemer, R. L., and Truszkowski, R.: Factors Affecting Human Potassium Tolerance, *Proc. Soc. Exper. Biol. & Med.* **35**:424-426 (Dec.) 1936.

77. Greene, J. A.; Levine, H., and Johnston, G. W.: Is the Potassium Tolerance Curve of Value in the Diagnosis of Adrenal Cortical Insufficiency in Man? *Endocrinology* **27**:375-377 (Sept.) 1940.

In considering the problems associated with the diagnosis of Addison's disease, it is necessary to bear in mind the fact that none of the procedures mentioned deals with the anatomic status of the adrenal cortex. This structure appears to have large margins of safety; a considerable portion of cortical substance must be destroyed before adrenal cortical insufficiency will occur. Before this degree of destruction takes place, the disease probably is essentially asymptomatic (with the possible exception of pigmentation), and any test based on adrenal cortical function may yield indecisive results.

Finally, there is often no decisive way of distinguishing atrophy from tuberculosis of the adrenal cortex except by the presence of calcification of the adrenal regions as seen in roentgenograms. The absence of calcification, however, does not exclude tuberculosis of the adrenal cortex. The latter condition can be inferred if tuberculosis can be demonstrated elsewhere in the body.

TREATMENT OF ADDISON'S DISEASE

Treatment of uncomplicated Addison's disease is directed primarily toward correction of the disturbances in metabolism of water and of electrolytes. This can be accomplished either by the administration of sufficient sodium to compensate for the loss in the urine or by preventing this loss through administration of adrenal cortical substances. Generally, a combination of the two methods is used. The administration of 10 Gm. of sodium chloride in addition to that in the diet may be sufficient to control most of the symptoms of patients who have a mild form of this disease. Better results are obtained, however, if sodium chloride is supplemented⁷⁸ with sodium lactate, sodium citrate or sodium bicarbonate. Wilder and his associates¹⁸ have shown that restriction of the intake of potassium facilitates treatment with sodium salts. In a review of the clinical course of illness of 110 patients having Addison's disease who were seen at the Mayo Clinic between 1933 and 1940, Hampton and one of us (E. J. K.)⁷⁹ discussed the results of different therapeutic regimens which were followed during this seven year period. It was apparent that the restriction of the intake of potassium together with the use of extra sodium chloride gave definitely better therapeutic results than when the intake of potassium was unrestricted.

Until recently the only adrenal cortical substances which were available for clinical use were various commercial adrenal cortical extracts. Although these extracts vary considerably in potency, they have one common property: that is, large amounts can be administered with comparative safety. The optimal dose varies with the intake of electrolytes and has to be determined in a given case chiefly by trial and error.

78. Footnotes 10 *a* and *b*.

79. Hampton, H. P., and Kepler, E. J.: Addison's Disease: Treatment and Prognosis, *Am. J. M. Sc.* **202**:264-271 (Aug.) 1941.

Thompson⁸⁰ frequently administered from 10 to 30 cc. daily⁸¹ and much larger amounts in isolated instances. Most physicians, however, employed smaller doses. Because patients found that the cost of treatment was burdensome or prohibitive, there was a tendency to use the least possible amount of extract that would prevent frank crisis. The patient's margin of safety, therefore, was narrow, and in spite of the combined treatment crises were relatively frequent. Overtreatment was practically unheard of. Occasionally a patient noted dependent edema, but usually this was of no great consequence.

In 1939 desoxycorticosterone was introduced for clinical use. Shortly thereafter⁸² résumés of excellent therapeutic results were reported independently by a number of investigators. This substance decreases the excretion of sodium and increases the excretion of potassium. A rapid restoration both of the volume and of the chemical constituents of the blood and extracellular fluids follows.⁸³ These effects are augmented by increased intake of sodium and diminished by an increased intake of potassium. Desoxycorticosterone has the great advantage of being uniformly potent. In addition, the cost of its use, as measured by the expenditure of money required to rehabilitate the patient, is considerably less than that of most cortical extracts. On the other hand, like insulin and thyroxine, it has the great disadvantage of being a double-edged weapon. Only a short time after its introduction reports began to appear which demonstrated that overdosage was dangerous, and sometimes fatal.⁸⁴ Usually the chief symptoms of overdosage were those that might be expected from theoretic considerations, namely, hypertension, cardiac embarrassment and edema of varying degree. Even massive anasarca has been reported. The chemical changes in the plasma may be the antithesis of those which occur in adrenal cortical insufficiency. There were also reports of sudden death attributed to use of desoxycorticosterone which occurred when the patient seemingly was getting along satisfactorily. These were often attributed, usually for want of a better explanation, to hypoglycemia.⁸⁵ In addition to these

80. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III, and Hoffman, W. S.: The Treatment of Addison's Disease with Adrenal Cortex Extract, *Endocrinology* **24**:774-797 (June) 1939.

81. Thompson, W. O.: Therapeutic Symposium: Discussion, *J. Clin. Endocrinol.* **1**:83-84 (Jan.) 1941.

82. Wilder, R. M.: Progress in Treatment of Addison's Disease, *Proc. Staff Meet., Mayo Clin.* **15**:273-277 (May 1) 1940.

83. (a) Thorn, G. W.: Adrenal Cortical Hormone Therapy, *Am. J. M. Sc.* **197**:718-729 (May) 1939. (b) Footnote 62 *c, d, e* and *f*.

84. Ferrebee and others.^{62b} Willson, Rynearson and Dry.^{63a} Wilder.⁸² Thorn.^{83a}

85. Sudden death frequently occurred in cases of Addison's disease prior to the introduction of any form of replacement therapy. There is a strong temptation to attribute these deaths to hypoglycemia. The available evidence, however, does not warrant this assumption.

practical considerations, desoxycorticosterone acetate has the theoretic disadvantage of failing to correct all the abnormalities which are observed during experimental cortical insufficiency. In other words, its administration does not constitute complete replacement therapy.⁸⁶ However, in many instances, when the drug is used properly, it is difficult to demonstrate the residual symptoms which might be expected if the therapy were not reasonably complete.

The administration of desoxycorticosterone acetate does not eliminate the necessity for the controlled intake of electrolytes. Of these sodium is the most important. No hard and fast rules have been formulated as to the optimal amount of table salt which should be added to the diet. In determining the dose of desoxycorticosterone acetate, common sense suggests that the intake of sodium chloride should be kept constant while the dose of the drug is being varied. The intake of potassium is less important, provided that it is adequate in amount. Loeb and his associates⁸⁷ found that the concentration of potassium in the serum both of men and of dogs could be reduced to abnormally low values by administration of desoxycorticosterone acetate and restriction of the intake of potassium. Furthermore, Tooke, Power and one of us (E. J. K.)⁸⁸ showed that patients treated with desoxycorticosterone acetate could tolerate relatively large amounts of potassium. It appears, therefore, that the low potassium, high sodium intake which proved so useful in the treatment of patients having Addison's disease before the advent of desoxycorticosterone acetate is not only unnecessary but actually dangerous when this drug is being administered.

The use of desoxycorticosterone acetate, therefore, greatly intensifies a problem which has been present ever since replacement therapy was first used in the treatment of Addison's disease, namely, that of evaluating response to treatment. Unfortunately, no satisfactory and comparatively simple single criterion (comparable, for example, to urinalysis for sugar or the determination of the basal metabolic rate) has been developed by which response to therapy can be determined with certainty. Various indirect procedures have been advocated. Among these are determination of venous blood pressure, roentgenologic determination of the size of the heart, electrocardiographic study, measurement of

86. Gordon, E. S.: The Use of Desoxycorticosterone and Its Esters in the Treatment of Addison's Disease, *J. A. M. A.* **114**:2549-2551 (June 29) 1940. Kendall.⁶⁶ Thompson.⁸¹

87. Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effect of Desoxycorticosterone Esters in Dogs, *Science* **90**:496-497 (Nov. 24) 1939. Ferrebee and others.^{62h}

88. Tooke, T. B., Jr.; Power, M. H., and Kepler, E. J.: The Tolerance of Patients Suffering from Addison's Disease to Potassium While Such Patients Are Being Treated with Desoxycorticosterone Acetate, *Proc. Staff Meet., Mayo Clin.* **15**:365-368 (May 1) 1940.

pulmonary vital capacity, hematocrit reading of the blood, measurement of the volume of blood and of extracellular fluid and chemical determination of plasma electrolytes. All of these appear to be either uncertain or too complex, or both, and their multiplicity testifies to their inadequacy. Most physicians who decide to use this drug for the treatment of Addison's disease, therefore, will have to be guided by such factors as sense of well-being, weight, blood pressure and the presence or absence of edema. As a general rule, it appears advisable to limit the dose to the least amount that is necessary to establish a sense of well-being. In this connection it should be emphasized that the intensity of Addison's disease, like that of many endocrine disorders, varies greatly in different patients and in the same patient at different times. Tuberculosis of the adrenal glands slowly advances from the medulla to the cortex. Islets of healthy tissue may remain, proliferate and even become adenomatous. Less is known about cortical atrophy, but it, too, probably progresses slowly. In either case and in any event the severity of disease is a variable. Consequently, even though the majority of patients have a fairly uniform response to a given dose of desoxycorticosterone acetate, an occasional patient fails to exhibit the expected degree of clinical improvement, while others readily show signs and symptoms of overtreatment. Furthermore, although the biochemical results of overtreatment are practically the antithesis of those of undertreatment, yet at times the clinical pictures of these two conditions may, confusingly enough, present in common such symptoms as weakness, nausea and vomiting.⁸⁹ Fortunately, however, such signs as an elevated venous pressure (grossly determined by the distance above the heart at which the peripheral veins collapse), subcutaneous edema, cardiac enlargement or hypertension,⁸⁹ which all point toward excessive accumulation of extracellular fluids, make for realization that too much desoxycorticosterone acetate or sodium or not enough potassium has been given. In short, the therapeutic effects of desoxycorticosterone acetate depend on the dose, the intake of potassium, the intake of sodium and the patient himself. Signs of overtreatment consequently may occur as the result of variations in any of these four factors, even though the actual dose of desoxycorticosterone did not appear to be particularly excessive. Occasionally patients are seen in a state of extreme cardiac embarrassment because of overtreatment. This represents as grave a medical emergency as the crisis of insufficiency. Its management con-

89. An apparently benign and asymptomatic type of essential hypertension may develop and persist without evidence of overtreatment. This type of hypertension is not directly related to increase in volume of extracellular fluid. (Roth, G. M.; Robinson, F. J., and Wilder, R. M.: Response of the Blood Pressure to the Cold Pressor Test in Addison's Disease During Treatment with Desoxycorticosterone Acetate, *J. A. M. A.* **116**:2429-2430 [May 24] 1941).

sists of those measures which remove the excess sodium, chloride and water from the body and relieve the strain on the circulatory system, that is, phlebotomy and the administration of mercurial diuretics, oxygen and digitalis.

The usual method of administering desoxycorticosterone acetate is by subcutaneous or intramuscular injection of the crystalline material dissolved in oil. As yet no case of serious infection resulting from the injection of this oily solution has been reported, nor has the incidence of hypersensitivity to the oily vehicle been a problem. The usual dose has been 1.5 to 5 mg. per day,⁹⁰ although some workers have obtained good results with considerably higher doses. Pellets of desoxycorticosterone acetate implanted subcutaneously have been shown by Thorn and his associates⁹¹ to be effective in supplying the patient having Addison's disease with a continuous source of desoxycorticosterone acetate. This has both the theoretic advantage of simulating the more or less continuous secretion of the adrenal gland and the practical advantage of eliminating for the most part daily injections. Some cases have been reported in which the clinical response to desoxycorticosterone acetate in the form of implanted pellets was better than the response to daily parenteral administration. Before implantation of pellets of desoxycorticosterone acetate is undertaken, the necessary daily dose of desoxycorticosterone acetate should be determined accurately. Observations should be of sufficient duration to determine any decrease in the patient's required dose or any symptoms of overtreatment which might not become manifest until several weeks of treatment had elapsed. The effectiveness of a given amount of desoxycorticosterone acetate implanted obviously depends, too, on the speed with which the pellets dissolve. Rate of dissolution is dependent on such physical characteristics as compactness, shape and size. Use of pellets is still in the experimental stage.

A more recently developed method of administration of desoxycorticosterone acetate, which has many of the advantages derived from implantation of pellets, is the oral administration of the crystalline material dissolved in propylene glycol.⁹² This solution is preferably administered sublingually several times a day. The dose varies roughly from one

90. Thorn, G. W.: Treatment of Addison's Disease, *J. Clin. Endocrinol.* **1**:76-81 (Jan.) 1941.

91. Thorn, G. W.; Howard, R. P.; Emerson, K., Jr., and Firor, W. M.: Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxy-Corticosterone Acetate): Implanted Subcutaneously, *Bull. Johns Hopkins Hosp.* **64**:339-365 (May) 1939.

92. Anderson, E.; Haymaker, W., and Henderson, E.: Successful Sublingual Therapy in Addison's Disease, *J. A. M. A.* **115**:2167-2168 (Dec. 21) 1940. Turnoff, D., and Rowntree, L. G.: Successful Sublingual Therapy in Addison's Disease, *ibid.* **116**:2016 (May 3) 1941.

and a half to five times the parenteral dose.⁹³ Since absorption of desoxycorticosterone from the oral route is less certain than that from the parenteral route, oral administration had best not be depended on during acute illness, especially when gastrointestinal disturbances are present.

For the treatment of acute adrenal insufficiency most writers agree that the administration of cortical extract is preferable to the use of desoxycorticosterone acetate. The extract may be given intravenously in amounts varying from 30 to 100 cc.

COMMENT

In this review we have devoted our attention chiefly to what is known about Addison's disease. What is not known is of equal importance; for example, the fundamental *modus operandi* of the adrenal cortical substances still remains a mystery. The site of their action is still debatable. The connecting link between the disruption of electrolyte metabolism, on the one hand, and the abnormalities of carbohydrate metabolism, on the other, has yet to be demonstrated. These are only a few of the obvious gaps in present day knowledge.

93. Hampton, H. P., and Kepler, E. J.: Addison's Disease: Treatment and Prognosis, *Am. J. M. Sc.* **202**:264-271 (Aug.) 1941.

DISEASES OF THE ADRENAL GLANDS

II. TUMORS OF THE ADRENAL CORTEX, DISEASES OF THE ADRENAL MEDULLA AND ALLIED DISTURBANCES

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Adrenal cortical tumors and allied disturbances¹ continue to arouse considerable interest. Since the last review of the subject appeared in this journal² a considerable number of cases have been reported and several comprehensive articles dealing with these conditions have appeared.³

TUMORS OF THE ADRENAL CORTEX

It is surprising, however, to find that no one has catalogued the symptoms as they have been described in the reports of cases which have been published. We have felt for a long time that some such work should be undertaken, because the various individual cases do not always conform, by any means, to the composite picture which has been so frequently described. Furthermore, there has been a tendency to use the "classic" case as the basis for endocrine hypotheses and implications which are not limited to this particular subject, but which bear on other

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1. This group of conditions is frequently discussed under the term adrenogenital syndrome, with the implication that there is a pathologic mechanism which is common to the group.

2. Kepler, E. J.: Diseases of the Adrenal Glands: A Review with Special Reference to the Clinical Aspects, *Arch. Int. Med.* **56**:105-135 (July) 1935.

3. (a) Grollman, A.: *The Adrenals*, Baltimore, Williams & Wilkins Company, 1936. (b) Haymaker, W., and Anderson, E.: Syndrome Arising from Hyperfunction of Adrenal Cortex: Adrenogenital and Cushing's Syndromes—A Review, *Internat. Clin.* **4**:244-299 (Dec.) 1938. (c) Kepler, E. J.: Tumors of the Suprarenal Cortex, Basophilic Tumors of the Pituitary Body, and Allied Diseases, in Philadelphia, F. A. Davis Company, 1939. (d) Kessel, F. K.: Morbus Piersol, G. W., and Bortz, E. L.: *Cyclopedia of Medicine, Surgery and Specialties*, Cushing: Ein Überblick über Klinik und Kasuistik des basophilen Hypophysenadenoms, *Ergebn. d. inn. Med. u. Kinderh.* **50**:620-678, 1936. (e) Wintersteiner, O.: Glandular Physiology and Therapy: The Adrenogenital Syndrome, *J. A. M. A.* **116**:2679-2683 (June 14) 1941. (f) Pico Estrada, O. M.: El diagnóstico de los tumores suprarrenales, Buenos Aires, El Ateneo, 1940.

current endocrinologic problems as well. With these thoughts in mind, we therefore reviewed all cases which we were able to find. The remarks which follow deal with some of the impressions that were obtained from this study.

To orient the reader who has not been particularly interested in this subject, it is necessary to point out that the various clinical syndromes which have been found to be associated with adrenal cortical tumor are conditioned by the sex of the patient and the period in the life history of the patient during which the tumor exerts its hormonal-like influences. Thus, the clinical picture differs among infants, boys, girls, men and women. In addition to those symptoms which are related to the sexual sphere, a group which may be called "metabolic," or "general," occur in varying degrees among persons of both sexes; they are not dependent on age and are essentially the same as those which occur in cases of Cushing's disease.⁴ It appears plausible that the variations in the differentiation and maturity of the neoplastic cells may be factors of importance responsible for the variations in the clinical pictures which are encountered among persons of the same sex of comparable ages. Goormaghtigh,⁵ for example, demonstrated cytologic and histologic differences in two tumors. One occurred in a feminized man, the other in a virilized woman. He was able to correlate these differences with assays of androgens and estrogens in the urine.

Reports⁶ of cases in which endocrine symptoms are minimal or absent continue to appear, although in some instances it is difficult to be

4. Considerable confusion has arisen because of the terms "Cushing's syndrome" and "Cushing's disease." In this paper we have adopted the suggestion of Kessel and have applied the term "Cushing's syndrome" to the clinical picture described by Cushing under the term pituitary basophilism and the term "Cushing's disease" to the condition in which this clinical picture is associated with a basophilic adenoma of the anterior lobe of the hypophysis.

5. Goormaghtigh, N.: The Cytology of Functioning Adrenal Cortex Tumors, *Am. J. Cancer* **38**:32-40 (Jan.) 1940.

6. (a) Bocca, C. R.: *Eléphantiasis nostras et tumeur de la surrénal*, *Lyon méd.* **158**:402-407 (Oct. 11) 1936. (b) Eliason, E. L.: Cortical Adrenal Tumors, *Internat. Clin.* **2**:221-229 (June) 1938. (c) Fernblatt, H. M., and Alkert, B.: Adenoma, Adenocarcinoma of the Adrenals, Based on a Series of Thirty-Four Cases, *New York State J. Med.* **37**:861-864 (May 1) 1937. (d) McGavack, T. H.: Masculinizing and Non-Masculinizing Carcinomata of the Cortex of the Adrenal Gland: Report of Six Adult Cases, *Endocrinology* **26**:396-408 (March) 1940. (e) Carcinoma of Adrenal, Cabot Case 23121, *New England J. Med.* **216**:519-521 (March 25) 1937. (f) Nettrour, W. S.: Angioma of the Liver with Adenocarcinoma of the Suprarenal Gland: Report of Two Cases, *Proc. Staff Meet., Mayo Clin.* **11**:710-713 (Nov. 4) 1936. (g) Puig, R.: *Corticossurrénalome malin avec*

certain on the basis of published data that the adrenal cortex represented the primary source of the neoplasm.^{6c} There is no question, however, that apparently "functionless" adrenal cortical neoplasms do occur. Some of these tumors, both with and without endocrine symptoms, have been highly malignant, rapidly growing neoplasms with a tendency to invade the renal veins and the vena cava and to metastasize to the liver and lungs.⁷ Others have been relatively benign and encapsulated. In this connection the large number of adrenal cortical adenomas which are encountered accidentally in the course of routine necropsy is significant. In such instances there usually has not been any evidence during life that endocrine disease was present.

General, or Metabolic, Symptoms.—Among the symptoms which are unrelated to the age and sex of the patient and which occur among patients suffering either from Cushing's disease or from adrenal cortical tumor are the following: obesity or a change in the distribution of fat; hypertension; osteoporosis; purplish striations of the skin; acne; polycythemia; diabetes or changes in carbohydrate metabolism, and fatigue. In addition, there may be present in cases of adrenal cortical tumor those local and generalized phenomena which might occur as the result of any expanding malignant and metastasizing intra-abdominal mass. All these "general" symptoms are variable; any or all of them have been absent, and almost every combination of them has been found in individual instances.

Extreme obesity has not been encountered frequently in cases of proved adrenal cortical tumor. Exceptions occur, of which an example is the case of an infant recently reported by Marks, Thomas and Warkany.⁸ Gain in weight, however, is a common symptom, and even when actual increase in weight has not occurred there may be a change in the distribution of adipose tissue. Marks and his associates⁸ investigated the occurrence of obesity among 24 children who had adrenal cortical tumor as reported in the literature. They stated: "In spite of their monstrous appearance the actual weight of the children with tumors of the adrenal cortex may not be much greater than the average."

In the classic case, the obesity is confined to the face, trunk and abdomen. The extremities remain thin. The full moonlike face, the

métastases multiples et fièvre ondulante, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:194-197 (Feb. 22) 1937. (h) Ravoire, J., and Guibert, H. L.: Adénome cortical d'une capsule surrénale (Etude anatomo-clinique), Ann. d'anat. path. **16**: 234-239 (Feb.) 1939. (i) Shenstone, N. S., and Loughheed, G. W.: Primary Cortical Carcinoma of the Suprarenal, Canad. M. A. J. **34**:188-189 (Feb.) 1936.

7. Wu, S. D.: Carcinoma of Adrenal Cortex, Chinese M. J. (supp.) **3**:52-93 (March) 1940.

8. Marks, T. M.; Thomas, J. M., and Warkany, J.: Adrenocortical Obesity in Children, Am. J. Dis. Child. **60**:923-942 (Oct.) 1940.

pad of fat high in the dorsal region and the other changes which occur in the distribution of fat produce a characteristic habitus. By no means all patients conform to this standard pattern. In the case reported by French⁹ the patient was emaciated; in that recorded by Lightwood¹⁰ the patient, although wasted, retained conspicuous deposits of fat about the face and chest. Two patients that we have seen had full faces but otherwise were not obese. Several instances have been reported in which no change in weight was apparent.

An increase in blood pressure occurred in many cases of adrenal cortical tumor. Both the systolic and the diastolic pressure were affected. This symptom appears to occur as frequently among children as among adult persons. In the case reported by Mainzer,¹¹ death resulted at the age of 8½ years, from a cerebrovascular accident that occurred after prolonged and severe hypertension. In some instances in which hypertension was marked the appearance of the ocular fundi was not unlike that in cases of essential hypertension. On the other hand, a number of cases have been reported in which hypertension was either minimal or absent.

Osteoporosis with pseudofractures (Looser's zones) occurs fairly commonly. Actual pathologic fractures have even been found. Because osteoporosis has been absent in many cases of adrenal cortical tumor, some authors have concluded erroneously that the presence of osteoporosis is diagnostic of Cushing's disease and that the possibility of adrenal cortical tumor could be excluded on this basis.

Striking abnormalities in the skin frequently have been associated with adrenal cortical tumor. In many instances the skin of the entire body became mottled, with unusual dusky purplish red areas, somewhat similar to those seen in cases of *cutis marmorata* or *livedo racemosa*. This mottling was most noticeable in the extremities and was designated as cyanosis in many of the published reports. The face usually was less mottled and its color more uniformly high than that of the rest of the body and sometimes resembled that seen in cases of *polycythaemia vera*. Acne was one of the most frequently mentioned of all the symptoms. It varied in severity from a few comedones to an intense eruption involving all the body except the abdomen and extremities and simulated the severe pustular types, such as *acne cachecticorum*, *acne aggregata seu conglobata* and *pyoderma faciale*. One of the most impressive of the abnormalities which accompany adrenal cortical tumor has been the purplish

9. French, H.: *An Index of Differential Diagnosis of Main Symptoms by Various Writers*, ed. 3, New York, William Wood & Company, 1922, p. 408.

10. Lightwood, R.: Tumour of the Suprarenal Cortex in an Infant of Eighteen Weeks, *Arch. Dis. Childhood* **7**:35-42, 1932.

11. Mainzer, F.: Nebennierenrindensyndrom mit arterieller Hypertension, *Acta med. Scandinav.* **87**:50-64, 1935.

striae atrophicae. These were noted chiefly on the abdomen, buttocks, thighs and arms. They may be 1 cm. or more in width and 10 cm. or more in length, tend to be depressed below the level of the rest of the skin and often are roughly parallel. They are apparently not to be attributed to changes in the weight of the patient or to stretching of the skin, because they have been encountered in instances in which the skin could not possibly have been stretched by a gain in weight. In a few reported cases the striae became infected. Ecchymoses, petechiae and hemorrhagic areas have been noted in some cases and extensive areas of keratosis pilaris in others. Recently, Albright and his associates¹² suggested that the changes observed in the skin are to be ascribed to a "thinning" produced by depletion of protein. We have difficulty in agreeing with this explanation.

Frank diabetes has not occurred as commonly as might be expected from the recent experimental work which indicates a close relation between the adrenal cortex and the metabolism of carbohydrates. However, minor disturbances in carbohydrate metabolism, such as alterations in the shape of the dextrose tolerance curve, frequently have been encountered. Lukens, Flippen and Thigpen¹³ reviewed data concerning carbohydrate metabolism in 44 cases of adrenal cortical tumor and 11 cases of bilateral adrenal cortical hyperplasia reported between 1917 and 1935. No impairment of carbohydrate metabolism was noted in 24 cases of tumor and in 4 cases of hyperplasia. Impaired carbohydrate utilization, as measured by dextrose tolerance, occurred without glycosuria in 3 cases of tumor. Transitory glycosuria accompanied tumor in 4 cases and hyperplasia in 1 case, and marked glycosuria was encountered in 13 cases of tumor and in 6 cases of hyperplasia. Wilder and one of us (E. J. K.),¹⁴ in 1938, reported a study of the carbohydrate metabolism of 8 patients suffering from adrenal cortical tumor. Definite diabetes was present in 1 instance and abnormal carbohydrate metabolism in 4 others. Shepardson and Shapiro,¹⁵ in 1939, could find only 17 cases which they were willing to accept as proved instances of adrenal

12. Albright, F.; Parson, W., and Bloomberg, E.: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis: Results of Treatment with Testosterone Propionate, *J. Clin. Endocrinol.* **1**:375-384 (May) 1941.

13. Lukens, F. D. W.; Flippen, H. F., and Thigpen, F. M.: Adrenal Cortical Adenoma with Absence of the Opposite Adrenal, *Am. J. M. Sc.* **193**:812-820 (June) 1937.

14. Kepler, E. J., and Wilder, R. M.: Disturbances of Carbohydrate Metabolism Observed in Association with Tumors of the Adrenal Cortex, *Acta med. Scandinav.* **90**:87-96, 1938.

15. Shepardson, H. C., and Shapiro, E.: The Diabetes of Bearded Women (Suprarenal Tumor, Diabetes and Hirsutism), *Endocrinology* **24**:237-252 (Feb.) 1939.

cortical tumor associated with diabetes; to this number they added a case of their own. They emphasized that diabetes occurs only occasionally in the presence of adrenal cortical tumor and presented evidence for the concept that the adrenal cortex cannot be regarded as solely responsible for the imbalance of carbohydrate metabolism in cases of adrenal cortical tumor with diabetes. These authors concluded: "It seems probable, however, that the anlage of diabetes must be present in those patients who develop the Achard-Thiers symptom-complex."¹⁶ We are inclined to concur with this concept of the relation between adrenal cortical tumor and diabetes.

Josephson¹⁷ reported the case of a 43 year old woman who had hirsutism, osteoporosis and severe diabetes. Subsequently the diabetes disappeared and Addison's disease supervened. Four months later severe diabetes reappeared. An adrenal cortical tumor was surgically removed, but the patient died of acute adrenal cortical insufficiency after the operation. Sprague¹⁸ recently observed a patient in whom severe diabetes, at times requiring the administration of more than 100 units of insulin daily for control, disappeared completely after removal of a huge adrenal cortical tumor. No other endocrine symptoms were observed in this patient. To our knowledge, this is the first instance in which diabetes has been the sole symptom of adrenal cortical tumor.

A number of authors have observed polycythemia of varying degree in association with adrenal cortical tumor. In the case of a patient we recently observed study of the blood by a hematologist disclosed all the characteristics of polycythaemia vera. In passing, it is worthy to note that the cause of the petechiae and hemorrhagic tendencies encountered among some patients with adrenal cortical tumor remains a mystery.

Among the less significant symptoms which have been noted are fatigue and pain. Pain has been at times a misleading symptom because it has occurred on the side opposite that on which the tumor is located. Backache and nerve root pains that result from osteoporosis have tended to confuse interpretation of the distress of which some of the patients complain. Finally, in cases in which the condition is of long standing or in cases in which there has been a rapidly growing or metastasizing tumor, such symptoms as abdominal mass, anemia and cachexia may be present.

Symptoms Related to the Age and Sex of the Patient.—The growth of a child afflicted with a tumor of the adrenal cortex is likely at first to

16. Diabetes of bearded women. The term has been used so loosely that it has ceased to have a precise meaning. In this particular case the term probably is synonymous with the "adrenogenital syndrome."

17. Josephson, B.: A Case of Alternating Cushing's Syndrome and Cachexia, Nord. med. tidskr. **16**:1396-1401, 1938.

18. Sprague, R.: Personal communication to the authors.

be unduly rapid. The long bones increase in length, and the so-called bone age is advanced.¹⁹ Premature dentition has likewise been noted.^{19a} These changes are not characteristic of adrenal neoplasms but, as Gross^{19b} has pointed out, regularly accompany precocious sexual development caused by various endocrine disturbances.

Should the process continue long enough and precocious puberty take place, as has been the case, the epiphyses tend to ossify, the growth of the long bones ceases and the trunk continues to elongate. The result may be a dwarf with relatively short arms and legs and a skeletal framework somewhat suggestive of that of an achondroplastic dwarf. One such patient has been observed at the Mayo Clinic.²⁰ The nonspecific character of these changes is illustrated by Sacchi's²¹ case, in which the deformity just described accompanied *pubertas praecox* associated with an interstitial cell tumor of the testis.

Among girls heterologous *pubertas praecox* seems to be the rule. When this occurs puberty not only is premature but is more or less masculine. In spite of the predominance of masculine features, instances have been reported in which menstruation has occurred. Although it has been asserted that premature menstruation does not occur among girls who have adrenal cortical tumor, vaginal and presumably uterine bleeding was noted in at least 4 instances.²²

In most instances, when a young girl was affected by an adrenal cortical tumor, hair appeared on the pubes and subsequently on the face, thighs and the rest of the body. Sometimes the labia changed to the adult type. The clitoris usually hypertrophied. This hypertrophy was in some cases so excessive that it ultimately caused the clitoris to resemble a small penis.²³ In addition, in some instances the voice became deep and coarse, so that it resembled that of an adolescent boy.

19. (a) Fraser, I.: Precocious Puberty in a Boy of One Year, *Brit. J. Surg.* **27**:521-526 (Jan.) 1940. (b) Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood, *Am. J. Dis. Child.* **59**:579-628 (March) 1940.

20. The photograph of this patient was published in a previous article (Kepler, E. J., and Rynearson, E. H.: Diseases of the Adrenal Glands, *M. Clin. North America* **24**:1035-1056 [July] 1940).

21. Sacchi, E., cited by Weber.^{28g}

22. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, *Tr. Path. Soc. London* **56**:189-208, 1905. Cecil, H. L.: Hypertension, Obesity, Virilism and Pseudohermaphroditism as Caused by Suprarenal Tumors, *J. A. M. A.* **100**:463-466 (Feb. 18) 1933. Kepler, E. J.; Kennedy, R. L. J., and Davis, A. C.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, *Proc. Staff Meet., Mayo Clin.* **9**:169-182 (March 21) 1934. Kepler, E. J.; Walters, W., and Dixon, R. K.: Menstruation in a Child Aged Nineteen Months as the Result of Tumor of the Left Adrenal Cortex: Successful Surgical Treatment, *ibid.* **13**:362-366 (June 8) 1938.

23. Kreutzer, R.; Visillac, V. O.; Rivarola, J. E., and Vergnolles, M.: Consideraciones sobre un caso de síndrome interrenal, *Prensa méd. argent.* **24**:2306-2313 (Dec. 1) 1937.

Adrenal cortical tumor is a rarity among children of either sex. In 1939 Reilly, Lisser and Hinman²⁴ were able to collect from the literature only 40 cases in which the patients were girls.

Adrenal cortical tumors occur even less frequently among boys; to date we have knowledge of only 17 reported cases,²⁵ in 14 of which pathologic specimens were obtained either at necropsy or at operation. In the boys *pubertas praecox* was homologous; that is, puberty was essentially normal but premature. Usually hair appeared on the face, genitalia and body and the genitalia were enlarged. In some instances they attained adult size or were larger, and functioned accordingly. For example, spermatogenesis was noted in the cases reported by Lisser^{25l} and Linser.^{25k} Sexual function certainly occurred in the case described by Mainzer,¹¹ for the patient, a boy 8½ years old, was treated for acquired venereal infection. In the case reported by Josephson,²⁵ⁱ on the other hand, the patient had infantile genitalia, childish features and no pubic or axillary hair. The photographs which accompanied the

24. Reilly, W. A.; Lisser, H., and Hinman, F.: Pseudosexual-Precocity and the Adrenal Cortical Syndrome in Preadolescent Girls: Report of a Case, *Endocrinology* **24**:91-114 (Jan.) 1939.

25. (a) Adams, C. E.: A Case of Precocious Development Associated with a Tumor of the Left Suprarenal Body, *Tr. Path. Soc. London* **56**:208-212 (April) 1905. (b) Baldwin, J. F.: Adrenal Precocity: Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, *J. A. M. A.* **63**:2286-2287 (Dec. 26) 1914. (c) Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933. (d) Estiu, M., and Laborde, F. J.: Síndrome de hiper-interrenalismo en un niño, *Rev. Asoc. méd. argent.* **44**:423-426 (July-Aug.) 1931. (e) Fordyce, A. D., and Evans, W. H.: Suprarenal Virilism, with a Report of Two Cases: Pathological Notes, *Quart. J. Med.* **22**:557-563 (July) 1929. (f) Gordon, M. B., and Browder, E. J.: Suprarenal Carcinoma with Pubertas Praecox in a Boy Three Years of Age, *Endocrinology* **11**:265-278 (July-Aug.) 1927. (g) Guthrie, L., and Emery, W. d'E.: Precocious Obesity, Premature Sexual and Physical Development, and Hirsuties in Relation to Hypernephroma and Other Morbid Conditions, *Tr. Clin. Soc. London* **40**:175-202, 1907. (h) Harwood, J.: Right Hemihypertrophy and Pubertas Praecox, *Proc. Roy. Soc. Med.* **25**:951-958 (May) 1932. (i) Josephson, B.: The Adrenal Cortical Syndrome in a Case with Tumor from an Accessory Adrenal Gland, *Acta med. Scandinav.* **90**:385-396, 1936. (j) von Kup, J.: Ein neuer Beitrag zur Frage des Zusammenhanges zwischen Zirbel und Nebennierenrinde, *Beitr. z. path. Anat. u. z. allg. Path.* **100**:137-148, 1937. (k) Linser, P.: Ueber die Beziehungen zwischen Nebennieren und Körperwachstum, besonders Riesenwuchs, *Beitr. z. klin. Chir.* **37**:282-305, 1903. (l) Lisser, H.: Successful Removal of Adrenal Cortical Tumor Causing Sexual Precocity in a Boy Five Years of Age, *Tr. A. Am. Physicians* **48**:224-235, 1933. (m) Rowntree, L. G., and Ball, R. G.: Diseases of the Suprarenal Glands, *Endocrinology* **17**:263-294 (May-June) 1933. (n) Tschernobrow, E.: Ueber eine Geschwulst der Nebenniere bei einem 11-jährigen Knaben mit frühzeitiger Geschlechtsentwicklung, Thesis, Zurich, 1919. (o) Lightwood.¹⁰ (p) Mainzer.¹¹ (q) Fraser.^{19a}

report of this case suggest a curious combination of Fröhlich's and Cushing's syndromes.

In the great majority of recently reported cases of adrenal cortical tumor the patients were young women. The clinical picture usually was similar to that which occurs among girls before the age of puberty. The chief endocrine symptoms noted were amenorrhea, hirsutism of the male type, enlargement of the clitoris and development of a masculine habitus, with atrophy of the breasts and coarsening of the voice. Homosexual tendencies, loss of libido and loss of the distinctly feminine psychic characteristics occasionally have been reported.

We found a variation in the number and magnitude of these symptoms. In several instances, including 1 which we encountered at the Mayo Clinic,²⁶ amenorrhea was the only endocrine symptom present. On the other hand, in a case in which the condition was of fairly long standing, the woman was almost completely virilized. The case reported by Lukens and Palmer²⁷ is an example of complete virilism with none of the stigmas of Cushing's syndrome. In certain other cases the end result presented all the clinical characteristics of Cushing's syndrome, with no changes suggestive of reversal of sex. A patient with such characteristics recently was observed by us. The great majority of cases reported were distributed between these extremes, and all conceivable gradations between the extremes were represented.

Only a few cases have been reported in which the patient was an adult male. The reports which have received the most attention are those in which feminization occurred.²⁸ The most recent example of this group is the case reported by Levy Simpson and Joll^{28c} in 1938. Their patient was a 34 year old physician in whom the enlargement of the

26. Walters, W.; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, *Ann. Surg.* **100**:670-688 (Oct.) 1934.

27. Lukens, F. D. W., and Palmer, H. D.: Adrenal Cortical Virilism, *Endocrinology* **26**:941-945 (June) 1940.

28. (a) Bittorf, A.: Nebennierentumor und Geschlechtsdrüsenausfall beim Manne, *Berl. klin. Wchnschr.* **56**:776 (Aug. 18) 1919. (b) Holl, G.: Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen, *Deutsche Ztschr. f. Chir.* **226**:277-295 (July) 1930. (c) Levy Simpson, S., and Joll, C. A.: Feminization in a Male Adult with Carcinoma of the Adrenal Cortex, *Endocrinology* **22**:595-604 (May) 1938. (d) Lisser, H.: A Case of Adrenal Cortical Tumor in an Adult Male Causing Gynecomastia and Lactation, *ibid.* **20**:567-569 (July) 1936. (e) Mathias, E.: Ueber Geschwülste der Nebennierenrinde mit morphogenetischen Wirkungen, *Virchows Arch. f. path. Anat.* **236**:446-469, 1922. (f) Volini, I. F., and O'Brien, G. F.: Pluriglandular Syndrome Associated with Carcinoma of Right Suprarenal Gland, *M. Clin. North America* **18**:1367-1376 (March) 1935. (g) Weber, F. P.: A Note on the Causation of Gynaecomastia (Mammary Feminism), *Lancet* **1**:1034-1035 (May 29) 1926. (h) zum Busch, J. P.: Gynäkomastie bei Hypernephrom, *Deutsche med. Wchnschr.* **53**:323 (Feb. 18) 1927.

breasts, loss of libido and potentia and regression in size of the sexual organs led to the discovery of an adrenal tumor. Some improvement followed removal of the neoplasm, but the patient died of metastasis two years later.

A number of instances have been reported among men, as among women, in which no endocrine symptoms whatever were associated with a neoplasm of the adrenal cortex.²⁹ The only symptoms present in such instances were those which might occur in the presence of any retro-peritoneal mass adjacent to a kidney.

Elliott and Shallard³⁰ observed a man in whom the symptoms produced by an adrenal cortical carcinoma were those of Cushing's syndrome. Feminization did not occur.

Tenenbaum³¹ described a 13 year old girl in whom generalized neurofibromatosis accompanied precocious puberty, hirsutism, weakness and moon face. Removal of an adrenal cortical tumor was followed by regression of all symptoms, including the neurofibromatosis, but the recurrence of symptoms eighteen months later presumably indicated recurrence of the tumor. This case is doubly interesting in that a number of instances have been reported in which generalized neurofibromatosis accompanied tumors of chromaffin tissue of the adrenal medulla (see "Diseases of the Adrenal Medulla").

Adrenal Cortical Hyperplasia.—Closely related both to tumor of the adrenal cortex and to Cushing's disease is a condition which frequently has been referred to as adrenal cortical "hyperplasia." Although the writings of Broster and others³² a number of years ago aroused wide interest in this condition, recent literature has done little to clarify its significance. It is apparently neither a clinical nor a pathologic entity. So far as we can determine, the essential facts concerning it may be summarized as follows: At necropsy in an appreciable number of proved cases of Cushing's disease, the adrenal cortex has been found to be enlarged and presumably hyperplastic. In another group of cases in which the clinical picture is compatible with the diagnosis either of adrenal cortical tumor or of basophil adenoma of the pituitary body, hyperplasia of the adrenal cortex was the only macroscopic observation at necropsy. In a large number of instances in which exploration of the adrenal bodies was undertaken because of the presence of symptoms

29. Footnote 6 c and i.

30. Elliott, G. T., and Shallard, B. T.: Cushing's Syndrome, M. J. Australia **1**:390-393 (Feb. 26) 1938.

31. Tenenbaum, J.: Carcinoma of the Adrenal Cortex: Case Report, J. Urol. **42**:277-287 (Sept.) 1939.

32. Broster, L. R.: The Surgery of the Adrenal Cortex, Brit. J. Surg. **26**: 925-941 (April) 1939; The Differential Diagnosis of Cushing's Syndrome (Basophilism) of Pituitary or Adrenal Origin, Brit. M. J. **1**:425-428 (March 16) 1940. Broster and Vines.^{25c}

indistinguishable from those usually associated with adrenal cortical tumor, the only finding has been "hyperplasia" of the adrenal cortex. Three cases have been reported³³ in which the patient appeared clinically to have Cushing's syndrome and at necropsy was found to have a thymic tumor and hyperplastic adrenal glands.³⁴ Furthermore, the association of adrenal cortical hyperplasia with feminine pseudohermaphroditism has been noted too frequently for the association to be regarded as a coincidence.³⁵ It does not appear justifiable at present to assume that this association necessarily implies a causal relation. Those interested in this controversial subject are referred to the papers of Cahill,³⁶ Young³⁷ and Grollman.³⁸ Finally, it should be mentioned that at necropsy the adrenal cortex is found to be enlarged and presumably hyperplastic in a number of diversified conditions in which endocrine symptoms were known to be absent during the life of the patient.

Wilkins and his associates³⁸ recently reported a remarkable case in which a 3½ year old boy had pubertas praecox, mental retardation and a pronounced craving for salt. He died as the result of what appeared clinically and chemically to be a state of acute adrenal cortical insufficiency. Necropsy disclosed marked adrenal cortical hyperplasia, with complete derangement of the normal cortical architecture and replacement of the normal constituents of the androgenic cells. The normal cellular structure of the testes was similarly disturbed by the presence of the same type of cells. This case lends important support to the early

33. (a) Kepler, E. J.: Report of Four Cases, in Symposium: Polyglandular Dyscrasias Involving Abnormalities of Sexual Characteristics, Proc. Staff Meet., Mayo Clin. **8**:102-107 (Feb. 15) 1933. (b) Leyton, O.; Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus with Pluriglandular Disturbance, J. Path. & Bact. **34**:635-660, 1931.

34. There have been no additional cases of this syndrome reported since the last review in this journal.

35. Bosselman, H.: Intersex mit suprarenalem Virilismus (Knochenmarkentwicklung in dem hyperplastischen Nebennieren), Endokrinologie **19**:292-306 (Nov.) 1937. Miller, I. D., and Kenny, P. J.: A Case of Adrenal Cortical Hyperplasia, Associated with Pseudohermaphroditism, Brit. J. Surg. **27**:728-733 (April) 1940. von Neugebauer, cited by Lissner, H.: The Uni-Glandular Origin of Pleuriglandular Syndromes, Endokrinologie **5**:138-170 (Oct.) 1929.

36. Cahill, G. F.: Adrenogenital Syndrome and Adrenocortical Tumors, New England J. Med. **218**:803-815 (May 12) 1938.

37. Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, Williams & Wilkins Company, 1937; Prostates in Females: Relation to Adrenal Cortical Hyperplasia, Tr. Am. A. Genito-Urin. Surgeons **30**:281-290, 1937.

38. Wilkins, L.; Fleischmann, W., and Howard, J. E.: Macrogenitosomia Praecox Associated with Hyperplasia of the Androgenic Tissue of the Adrenal and Death from Corticoadrenal Insufficiency: Case Report, Endocrinology **26**:385-395 (March) 1940.

theories of Grollman³⁹ and others that the cells of the androgenic zone are distinct physiologically, as well as embryologically and cytologically. It would appear not only that the overgrowth of androgenic cells produced excessive quantities of virilizing substances but that the resultant derangement led to adrenal cortical insufficiency.

In recent years little light has been thrown on the problem of the large group of women who have varying degrees of hirsutism, which is sometimes associated with menstrual disturbances. Some of these women have a slightly masculine habitus. Others are obese. Still others appear to be entirely normal except that they are hairy. On the whole, such women are and appear to be healthy, and their problem is usually chiefly cosmetic. Except for the presence of hair they have few or none of the other symptoms of adrenal cortical tumor or Cushing's syndrome. They constitute a tragic and poorly understood group of patients. Some authors prefer to consider their condition as a form of adrenal cortical hyperplasia or "subclinical pituitary basophilism."⁴⁰ This concept recently has aroused wider interest, since it has been demonstrated that some of these women exhibit minor alterations in the urinary excretion of estrogens and androgens.⁴⁰ Notwithstanding, the histologic and physiologic bases for this assumption rest on exceedingly shaky foundations. It must still be admitted that practically nothing is known about the causation of the hirsutism of these patients. Incidentally, we have never seen beneficial results follow any form of therapy whatsoever. Mussio Fournier and associates⁴¹ reported the case of a patient which is an exception to the rule.

A curious syndrome associated with hyperplasia of the adrenal glands recently has been described which appears to bear little relation to the clinical states that have been discussed. Di Ruggiero and Jolly,⁴² in 1938, reported a case in which an infant died at the age of 4 weeks after persistent vomiting which simulated that of pyloric stenosis. The only observation at necropsy was pronounced adrenal hyperplasia ("chiefly medullary"). Dijkhuizen and Behr,⁴³ in 1940, reported 4 cases of a similar condition. In all cases an identical clinical picture was presented, with death occurring in the fourth to the sixth week after birth. In the 3 cases in which the results of necropsy were available, the only observation was tremendous hypertrophy of the adrenal glands (which weighed

39. Compare Wintersteiner's^{3e} comments regarding Grollman's present position on this point.

40. Glass, S. J., and Bergman, H. C.: Subclinical Adrenogenital Syndrome, *Endocrinology* **23**:625-629 (Nov.) 1938.

41. Mussio Fournier, J. C.; Albrieux, A. S., and Morato Manaro, J.: Acción local de las hormonas, *Arch. clín. e inst. de endocrinol.* **1**:39-56, 1937-1940.

42. Di Ruggiero, and Jolly, A.: Vomissements graves du nourrisson et hypertrophie des surrénals, *Ann. d'anat. path.* **15**:332-335 (March) 1938.

43. Dijkhuizen, R. K., and Behr, E.: Adrenal Hypertrophy in Infants: A New Clinical Entity of the Neonatal Period, *Acta pædiat.* **27**:279-295, 1940.

24, 22 and 34 Gm., respectively). The authors reported that the entire gland was hypertrophic, particularly the cortex, with overgrowth of such magnitude as to throw the surface into folds suggesting the sulci and gyri of brain tissue. In 2 of the 4 cases the condition occurred in siblings, 1 of whom, a male, was a pseudohermaphrodite. One is reluctant to assume that in these cases the hyperplasia of the adrenal cortex was coincidental. However, specific evidence that the hyperplasia of the adrenal cortex was a cause of the clinical picture is lacking in the accompanying data.

Diagnosis.—In the last review² evidence was cited that Cushing's syndrome is not specific for Cushing's disease but may occur in association with a number of pathologic processes, among which is tumor of the adrenal cortex. Since that time this assertion has been amply documented by a large number of case reports. Because of this lack of specificity the major obstacle in the diagnosis of an adrenal cortical tumor is elimination of Cushing's disease. Conversely, in the diagnosis of Cushing's disease the chief concern of the diagnostician is exclusion of tumor of the adrenal cortex. The problem of treatment renders this question of differential diagnosis of great importance, for the results of treatment of Cushing's disease with roentgen rays are uncertain and often disappointing, whereas, by contrast, successful removal of adrenal cortical neoplasms has been followed by results which are among the most spectacular in medicine. There is a school of thought (see Bland and Goldstein⁴⁴) which holds that unless there is unequivocal clinical evidence of an adrenal cortical tumor all patients who have Cushing's syndrome should receive roentgen ray therapy over the pituitary body because surgical exploration of the adrenal bodies is a great operative risk. Analysis of the reported cases, in our opinion, supports the opposite view: that in every case of a condition thought to be Cushing's disease, regardless of how typical it may seem, the patient should be examined with the suspicion in the physician's mind that the cause may be a surgically removable tumor of the adrenal gland.

Recent literature indicates widespread and generalized use of the procedure brought into favor by Cahill and associates,⁴⁵ in which the adrenal glands are delineated in roentgenograms by the injection of air into the perirenal fascial spaces.⁴⁶ In a considerable number of the

44. Bland, P. B., and Goldstein, L.: Pituitary Basophilism, Surg., Gynec. & Obst. **65**:644-656 (Nov.) 1937.

45. (a) Cahill, G. F.; Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M.: Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287-313 (Feb. 15) 1936. (b) Cahill.³⁶

46. (a) Hyman, A., and Wilhelm, S. F.: The Differential Diagnosis of Renal and Suprarenal Tumors, J. Urol. **40**:737-751 (Dec.) 1938. (b) Mencher, W. H.: Perirenal Insufflation, J. A. M. A. **109**:1338-1341 (Oct. 23) 1937. (c) Walters, W., and Kepler, E. J.: Surgical Lesions of the Adrenal Glands, *ibid.* **111**:1061-1065 (Sept. 17) 1938.

reported cases, evidence of adrenal tumor or of adrenal hyperplasia was obtained by this method when other methods gave negative results. Instances have been reported of collapse after perirenal insufflation (Hyman and Wilhelm),^{40a} and in at least 1 instance the development of emphysema after the insufflation of air interfered with subsequent surgical procedures (Lukens, Flippen and Thigpen).¹³ We have had little experience with this technic, but Cope and Schatzi⁴⁷ reported marked success and few untoward reactions in a large series of cases in which they employed a modification of Cahill's method. There seems to be little doubt that in the hands of careful and experienced surgeons the method is reasonably safe⁴⁷ and that it is capable of disclosing the presence not only of a gross lesion but of hyperplasia and small adrenal cortex adenoma. Negative results obtained by this method, however, cannot necessarily be regarded as conclusive.

In some centers—at the Mayo clinic, for example, surgical exploration remains the method of choice for determining the status of the adrenal glands. If the procedure is carried out by a competent surgeon the risk is slight, provided that both adrenal glands are not partially resected or damaged by rough handling. When the patient is a female, some surgeons still prefer to use an abdominal approach to visualize the ovaries at the same time. Others prefer a posterolumbar incision. The chief objection to the use of a major surgical procedure as a diagnostic aid is the fact that the patient may be greatly disappointed if a tumor is not found to account for his condition, even though such a possibility has been carefully and frankly stressed before the operation.

The most promising development in the diagnosis of hyperfunctioning lesions of the adrenal cortex in recent years has been the clinical application of assay of the urine for hormone-like substances. Earlier reports were concerned with biologic methods; more recent ones, with colorimetric determinations or chemical isolation of specific chemical compounds. The substances which have been investigated can be arranged in four categories: (1) estrogenic substances; (2) androgenic substances; (3) substances which prolong survival of adrenalectomized animals, and (4) inactive compounds related chemically to hormones. Excellent summaries of the literature pertaining to this subject have been published recently by Looney⁴⁸ and Wintersteiner.^{3e}

Estrogenic Substances: Kurzrok, cited by Cahill and others,^{45a} in 1930, found a large amount of estrogenic substance in the urine of a patient proved to have adrenal cortical tumor (case 2 of the series

47. Cope, O., and Schatzi, R.: Tumors of the Adrenal Glands: I. A Modified Air Injection Roentgen Technic for Demonstrating Cortical and Medullary Tumors, *Arch. Int. Med.* **64**:1222-1238 (Dec.) 1939.

48. Looney, J. M.: Sex Factors of the Adrenal Gland, *Endocrinology* **27**:511-520 (Sept.) 1940.

reported by Cahill and associates).^{45a} Results of the Aschheim-Zondek test for pregnancy were negative. Five days after removal of the tumor there was complete absence of estrogen from the urine. Frank,⁴⁹ in 1934, was the first to propose that the excretion of estrogenic substances in the urine might be of diagnostic value in the presence of carcinoma of the adrenal cortex. He found enormous quantities of estrogen in the urine of 4 women who had hyperfunctioning adrenal cortical tumor. Other cases in which values for estrogens were high have been reported by Graef, Bunim and Rottino⁵⁰ and by Lukens and Palmer.²⁷ McGavack^{6a} reported an increase in the urinary excretion of estrogens in a woman who had carcinoma of the adrenal cortex. He also reported normal values for estrogens and high values for androgens in the urine of a number of patients suffering from adrenal cortical hyperplasia.

Normal values for estrogen in the urine were found by Bruins Slot⁵¹ in a woman who had a hyperfunctioning adrenal cortical tumor. Walters and one of us (E. J. K.)⁵² were unable to demonstrate any increase in the excretion of estrogen in several of the cases in a series; in a case recently reported from the Massachusetts General Hospital, Boston,⁵³ only a slight elevation in the output of estrogen in the urine occurred.

Of particular interest are the determinations of estrogens in the urine of men in whom an adrenal cortical tumor is associated with evidences of feminization. Records of such cases are few, and in only 1, that reported by Levy Simpson and Joll in 1938,^{28c} are results of estrogen assays included. The case has been referred to elsewhere in this review. This patient excreted large amounts of an estrogenic substance, presumably estrone, before operation; this substance disappeared with regression of the feminine characteristics following surgical removal of the tumor but reappeared later with recurrence of the neoplasm and its symptoms.

Glass and Bergman⁴⁰ reported 2 cases in which feminization in males (gynecomastia and genital atrophy) apparently was not associated with tumor, a circumstance which they ascribed to adrenal cortical hyper-

49. Frank, R. T.: Suggested Test for Functional Cortical Adrenal Tumor, *Proc. Soc. Exper. Biol. & Med.* **31**:1204-1206 (June) 1934; A Suggested Test for Cortical Adrenal Carcinoma, *J. A. M. A.* **109**:1121 (Oct. 2) 1937.

50. Graef, I.; Bunim, J. J., and Rottino, A.: Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex: Indeterminate Pituitary Adenoma and Selective Changes in the Beta Cells (Basophils) of the Hypophysis, *Arch. Int. Med.* **57**:1085-1103 (June) 1936.

51. Bruins Slot, W. J.: The Relation of Sex Hormones in a Case of Virilism by Hypernephroma, *Acta med. Scandinav.* **89**:371-375, 1936.

52. Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment: A Study of Seven Operated Cases, *Ann. Surg.* **107**:881-898 (June) 1938.

53. Carcinoma of the Adrenal Cortex, Left with Metastases to Periaortic Nodes, Cabot Case 26261, *New England J. Med.* **222**:1086-1090 (June 27) 1940.

function. The androgen-estrogen ratio was definitely reduced in both these cases, in 1 because of an increased excretion of estrogens and in the other because of a diminished output of androgens.

Saphir and Parker⁵⁴ found an increased excretion of estrogens in a patient who presented the adrenogenital syndrome, with normal adrenal bodies and small nests of adrenal cortical cells in the ovaries. Lack of complete recovery after removal of the ovaries was attributed to the probable presence of similar nests elsewhere.

Androgenic Substances: The excretion in the urine of androgens by patients who exhibit symptoms suggestive of adrenal cortical hyperfunction has received more attention in recent years than has the excretion of estrogens. Koch⁵⁵ found an increase of the androgen-estrogen ratio of the urine in most, but not all, of the cases of virilism in his series; in most instances this was due not only to an increased output of androgens but to a decreased excretion of estrogens. Levy Simpson, de Fremery and Macbeth⁵⁶ found an excess of androgen in the urine of 4 of 7 women who had the adrenogenital syndrome, 3 women who had Cushing's syndrome and 2 of 3 girls who had pseudohermaphroditism. No excess of androgenic material was found in the urine of 3 women who had the adrenogenital syndrome, 1 woman more than 50 years old who had the Achard-Thiers syndrome and a pseudohermaphrodite 4 years old. Elevated values for the excretion of androgens in the urine have been noted by many authors, both for patients who have adrenal cortical tumor and for those in whom the same syndrome is associated with adrenal cortical hyperplasia. In some cases of tumor the excretion of androgens has been enormous. Dingemanse and Laqueur,⁵⁷ Callow⁵⁸ and Bruins Slot⁵¹ all reported values exceeding 2,000 international units per day.

An important contribution recently has been made by Crooke and Callow.⁵⁹ These authors studied 4 patients suffering from Cushing's

54. Saphir, W., and Parker, M. L.: Adrenal Virilism, *J. A. M. A.* **107**:1287-1288 (Oct. 17) 1936.

55. Koch, F. C.: Recent Studies on the Excretion of Male Sex Hormones in Man, *Ann. Int. Med.* **11**:297-301 (Aug.) 1937; *The Chemistry and Biology of Male Sex Hormones*, in Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938.

56. Levy Simpson, S.; de Fremery, P., and Macbeth, A.: The Presence of an Excess of 'Male' (Comb-Growth and Prostate-Stimulating) Hormone in Virilism and Pseudo-Hermaphroditism, *Endocrinology* **20**:363-372 (May) 1936.

57. Dingemanse and Laqueur, E.: Occurrence of Abnormally Large Quantities of Male Hormones in Urine of Patients with Suprarenal Tumor, *Nederl. tijdschr. v. geneesk.* **82**:4166-4170 (Aug. 27) 1938.

58. Callow, R. K.: The Significance of the Excretion of Sex Hormones in the Urine, *Proc. Roy. Soc. Med.* **31**:841-856 (Feb. 8) 1938.

59. Crooke, A. C., and Callow, R. K.: The Differential Diagnosis of Forms of Basophilism (Cushing's Syndrome), Particularly by the Estimation of Urinary Androgens, *Quart. J. Med.* **8**:233-349 (July) 1939.

syndrome, 2 of whom were proved to have basophil adenoma of the pituitary body and 2 tumor of the adrenal cortex. The 2 patients who had adrenal cortical tumor both excreted large quantities of androgenic material in the urine, whereas the patients who had basophil adenoma of the pituitary body excreted normal amounts. Should further investigation in other cases confirm this distinction, the importance of the observation as a diagnostic aid is obvious. Drips and Osterberg,⁶⁰ however, found normal values for the output of androgens in the urine of 3 women who had Cushing's disease but an increased amount in the urine of a man who had the same condition. McGavack⁶¹ reported normal values for androgens in the urine of a woman found at operation to have carcinoma of the adrenal cortex, and Mason⁶¹ likewise recorded normal values for androgens (5 micrograms per day) in the urine of a patient found to have adrenal cortical tumor.

Anderson, Haymaker and Joseph,⁶² using extracts of the blood and urine of 3 patients who had Cushing's syndrome, were able to prolong the survival of adrenalectomized animals. Similar extracts obtained from normal controls produced no such effect. The authors expressed the belief that this demonstrated the presence of excessive quantities of the adrenal cortical hormone in the blood and urine of these patients. On critical examination, however, the data of these investigators are not entirely convincing.

An increasing number of specific compounds, among them cresols, triols, steroids and allied substances, not all of which have shown hormonal activity, have been isolated from the urine of patients suffering from adrenal cortical tumor.⁶³ Several of these substances had not

60. Drips, D. G., and Osterberg, A. E.: An Evaluation of a Colorimetric and a Biologic Method for Determining Urinary Androgens, *Endocrinology* **27**: 345-354 (Sept.) 1940.

61. Mason, H.: Personal communication to the authors.

62. Anderson, E., and Haymaker, W.: Adrenal Cortical Hormone (Cortin) in Blood and Urine of Patients with Cushing's Disease, *Proc. Soc. Exper. Biol. & Med.* **38**:610-613 (June) 1938. Anderson, E.; Haymaker, W., and Joseph, M.: Hormone and Electrolyte Studies of Patients with Hyperadrenocortical Syndrome (Cushing's Syndrome), *Endocrinology* **23**:398-402 (Oct.) 1938.

63. Burrows, H.; Cook, J. W.; Roe, E. M. F., and Warren, F. L.: Isolation of Δ : 3:5 Androstadiene-17-one from the Urine of a Man with a Malignant Tumor of the Adrenal Cortex, *Biochem. J.* **31**:950-961 (June) 1937. Butler, G. C., and Marrian, G. F.: The Isolation of Pregnane-3, 17, 20-Triol from the Urine of Women Showing Adrenogenital Syndrome, *J. Biol. Chem.* **119**:565-572 (July) 1937; Chemical Studies on the Adreno-Genital Syndrome: The Isolation of 3 (α)-Hydroxyetiocholane-17-one, 3 (β)-Hydroxyetioallocholane-17-one (Isoandrosterone) and a New Triol from the Urine of a Woman with an Adrenal Tumor, *ibid.* **124**:237-247 (June) 1938. Kenyon, A. T.; Gallagher, T. F.; Peterson, D. H.; Dortman, R. I., and Koch, F. C.: The Urinary Excretion of Androgenic and Estrogenic Substances in Certain Endocrine States: Studies in Hypogonadism, Gynecomastia and Virilism, *J. Clin. Investigation* **16**:705-717 (Sept.) 1937. Koch.⁵⁵ Callow.⁵⁸

previously been found in tissue extracts. It seems reasonable to expect that further precise chemical recognition of the substances elaborated by adrenal cortical tumors offers the greatest likelihood of clarifying the pathologic physiology of this syndrome.

In summary, it would appear that some, but by no means all, patients who have adrenal cortical tumor excrete excessive quantities of estrogens. Many, but not all, patients suffering from adrenal cortical tumor excrete excessive quantities of "androgenic material." A few patients apparently excrete excessive quantities of both. A considerable variety of chemical compounds, some biologically active, others inert, have been isolated. Many of these have not been discovered in other material. In short, in cases of adrenal cortical tumor, the results of assays of urine for substances that possess hormonal properties have been about as variable as the clinical pictures encountered. These results are in keeping with the diversified histologic structure of adrenal cortical tumors. Nor are they surprising when one considers the histologic similarity, one to another, of cortical cells, luteal cells and the interstitial cells of the testes in conjunction with the chemical similarity of the various crystalline cortical steroids, the estrogens and the androgens.

As has been mentioned, adrenal cortical hyperplasia has in some instances been associated with clinical pictures which resemble in almost every detail those accompanying both adrenal cortical tumor and Cushing's disease. In such instances there is no means by which a positive differential diagnosis can be made except by direct surgical examination or by visualization of the hyperplastic cortex in roentgenograms after the insufflation of air.

In addition to the conditions which have been mentioned, the differential diagnosis of adrenal cortical tumor among children involves consideration of all the pathologic processes which result in sexual and somatic precocity. Among these are (1) various intracranial lesions (such as internal hydrocephalus,⁶⁴ pinealoma,⁶⁵ tumor of the third

64. Dorff, G. B., and Shapiro, L. M.: A Clinicopathologic Study of Sexual Precocity with Hydrocephalus: Report of Two Cases Occurring in Females, with Postmortem Examinations in One, *Am. J. Dis. Child.* **53**:481-499 (Feb.) 1937. Thomas, A., and Schaeffer, H.: Un cas de macrogénitosomie précoce avec hydrocéphalie, lésions inflammatoires de la région infundibulo-tubérienne et symphyse cervicale triméningée, sans néoplasme intracranien, *Rev. neurol.* **2**:595-606 (Nov. 5) 1931.

65. Bailey, P., and Jelliffe, S. E.: Tumors of the Pineal Body, with an Account of the Pineal Syndrome, the Report of a Case of Teratoma of the Pineal and Abstracts of All Previously Recorded Cases of Pineal Tumors, *Arch. Int. Med.* **8**:851-880 (Dec.) 1911. von Frankl-Hochwart, L.: Ueber Diagnose der Zirbeldrüsentumoren, *Deutsche Ztschr. f. Nervenhe.* **36-37**:455-465, 1909. Horrax, G.: Further Observations on Tumor of the Pineal Body, *Arch. Neurol. & Psychiat.* **35**:215-228 (Feb.) 1936. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, *ibid.* **13**:423-470 (April) 1925.

ventricle⁶⁶ and similar lesions in the region of the pituitary body), (2) interstitial cell tumor of the testes⁶⁷ and (3) arrhenoblastoma and granulosa cell tumor of the ovary.⁶⁸ Among adult persons one must also consider thymoma associated with adrenal cortical hyperplasia and arrhenoblastoma and possibly lutein cell tumor (Saphir).⁶⁹ The diagnosis in all of these instances may be relatively easy if physical examination discloses the presence of the tumor. We were unable to find reports of any special diagnostic methods applicable to these problems which already have not been discussed.

Pathologic Physiology.—Except for what clarification has resulted from assays of hormonal-like substances in the urine, as previously discussed, knowledge of the pathologic physiology of adrenal cortical tumor has not been materially advanced in the past few years.

Some authors have become so impressed with the diverse manifestations of adrenal cortical tumors that they have hypothesized the existence of two syndromes associated with such neoplasms. For example, Haymaker and Anderson,^{3b} in their recent review, suggested the term adrenogenital syndrome for the classic picture of adrenal virilism in which sexual alterations predominate and the term adrenocortical syndrome for the clinical picture of Cushing's syndrome. They suggested, incidentally, that the former probably represents excessive production by the adrenal cortex of an androgenic substance and the latter excessive production of the so-called essential, or vital, adrenal cortical hormone. Although it may be freely admitted that individual cases have been reported which serve as typical examples of the aforementioned extremes, the majority of cases fail to conform to such precise definition

66. Dods, L.: Adrenohypophyseal Dystrophies of Infancy and Childhood, *M. J. Australia* **2**:277-286 (Sept. 1) 1934. Héuyer, G.; Lhermitte, J.; de Martel, and Vogt, C.: Un cas de macrogénitosomie précoce liée à un épendymogliome de la région mamillo-tubérale, *Rev. neurol.* **2**:194-210, 1931. LeMarquand, H. S., and Russell, D. S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumor in the Floor of the Third Ventricle, *Roy. Berkshire Hosp. Rep.*, 1934-1935, pp. 31-61.

67. Stewart, C. A.; Bell, E. T., and Roehlke, A. B.: An Interstitial-Cell Tumor of the Testis with Hypergenitalism in a Child of Five Years, *Am. J. Cancer* **26**:144-150 (Jan.) 1936. Sacchi,²¹ Weber.^{28g}

68. Meyer, R.: The Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characteristics, *Am. J. Obst. & Gynec.* **22**:697-713 (Nov.) 1931. Novak, E.: Masculinizing Tumors of the Ovary (Arrhenoblastoma, Adrenal Ovarian Tumors), with Report of Six Additional Cases of Arrhenoblastoma, *ibid.* **36**:840-858 (Nov.) 1938. Novak, E., and Gray, L. A.: Clinical and Pathologic Differentiation of Certain Special Ovarian Tumors: Granulosa Cell Carcinoma, Arrhenoblastoma, Disgerminoma, Brenner Tumor, *ibid.* **31**:213-229 (Feb.) 1936.

69. Saphir, O.: So-Called Lutein Cell Tumors, *Am. J. Obst. & Gynec.* **37**:1008-1014 (June) 1939.

and as a group embrace virtually every conceivable combination of symptoms. In fact, survey of the accumulated mass of reports of cases impresses the observer with the striking pleomorphic character of the clinical pictures which have been encountered.

In our judgment, theories regarding the mechanisms which are responsible for the production of the various clinical syndromes will be of little value until the physiologic relations of the adrenal cortex have been clarified. For the time being, therefore, the problem rests largely with the physiologist and the biochemist rather than with the clinician.

It is remarkable that so few instances of hyperfunctioning adrenal cortical lesions have been encountered in which alterations of electrolyte metabolism could be demonstrated. Loeb^{45a} conducted chemical studies on many of Cahill's patients, with negative results, an experience shared by many investigators. The first instance in which changes in the electrolyte pattern of the blood were noted was reported by one of us (E. J. K.)^{33a} in 1933, and a second instance was added a few years later.⁷⁰ In both cases pronounced alkalosis was associated with a high value for plasma bicarbonate and a low concentration of plasma chloride. In 1937 McQuarrie, Johnson and Ziegler⁷¹ published the results of intensive metabolic studies in a case previously reported by Ulrich,⁷² in which the diagnosis of basophil adenoma of the pituitary was confirmed at necropsy. Disturbances of the pattern of plasma electrolytes in this case were in most respects diametrically opposite those found in a case of typical Addison's disease. The most striking abnormalities were the high concentration of bicarbonate and sodium and the decrease in potassium and chloride, which produced a persistent tendency toward alkalosis, in addition to the clinical features characteristic of Cushing's syndrome.

Goldzieher⁷³ has also reported a high value for plasma sodium and a low value for plasma potassium in the case of a woman past the period of the menopause who exhibited the picture of Cushing's syndrome, presumably caused by adrenal cortical tumor. He did not mention the presence of alkalosis or values for bicarbonate.

70. (a) Walters, W.; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases, with Successful Surgical Treatment, *Proc. Staff Meet., Mayo Clin.* **9**:400-407 (July 3) 1934. (b) Kepler.²

71. McQuarrie, I.; Johnson, R. M., and Ziegler, M. R.: Plasma Electrolyte Disturbance in Patient with Hypercorticoadrenal Syndrome Contrasted with That Found in Addison's Disease, *Endocrinology* **21**:762-772 (Nov.) 1937.

72. Ulrich, H. L.: A Basophilic Adenoma of the Pituitary Gland, *Minnesota Med.* **18**:73-77 (Feb.) 1935.

73. Goldzieher, M. A.: Adrenal Cortical Disturbances, *Internat. Clin.* **4**:20-39 (Dec.) 1939.

Willson, Power and one of us (E. J. K.)⁷⁴ recently reported a similar case in which the patient had Cushing's syndrome, presumably associated with a basophil adenoma of the pituitary. In this case, the chief chemical findings were diminished concentration of potassium and chloride, increased concentration of bicarbonate and an elevated p_H (alkalosis).⁷⁵ The concentration of sodium in the plasma in this case was not elevated. It is remarkable not that such phenomena have been observed in these instances but that in all the cases of so-called hypercorticoadrenalism such changes have been noted so rarely. It is equally remarkable that among the few cases in which "hypercorticalism" has been associated with disturbances of electrolyte metabolism there is, to our knowledge, not a single instance of proved adrenal cortical tumor.

Treatment.—There is general agreement that the treatment of an adrenal cortical tumor is surgical. If a tumor can be completely removed, the result is spectacular improvement. Except in instances of tumor among children, in which precocious epiphysial union may occasionally have produced irreversible dwarfism, and in certain instances in which facial hair has persisted,²⁷ the disappearance of symptoms usually is complete after total removal of the tumor. If the tumor has penetrated its capsule, eventual recurrence, either locally or in the form of widespread metastasis, is to be anticipated.

The hazard of removal of an adrenal cortical tumor, as judged by reports of isolated cases, appears to be distressingly great. On the other hand, reports⁷⁶ of series of cases have appeared in which a much more favorable impression is conveyed.⁷⁷ In many instances death is still attributed to postoperative "shock." A critical analysis of the fatalities leads us to believe that, in spite of statements to the contrary, death more often than not is the result of the occurrence of acute adrenal insufficiency. It is well known that in many cases of tumor of one adrenal cortex the opposite adrenal gland is atrophic. Even complete absence of the opposite gland has been reported by Lukens and associates¹³ and by

74. Willson, D. M.; Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in Case of Cushing's Syndrome: Metabolic Study, *J. Clin. Investigation* **19**:701-707 (Sept.) 1940.

75. In 2 of the 3 cases at the Mayo Clinic the magnitude of the alkalosis was sufficient to produce tetany.

76. Walters, Wilder and Kepler, footnotes 26 and 70 a. Cahill and others.^{45a}

77. Fifteen patients suffering from adrenal cortical tumor have been operated on at the Mayo Clinic to date. The only operative fatality in the entire group occurred in 1924, prior to the advent of modern methods for the treatment of adrenal cortical insufficiency (Keyser, L. D., and Walters, W.: Carcinoma of the Suprarenal Associated with Unusual Endocrine Manifestations, *J. A. M. A.* **82**: 87-88 [Jan. 12] 1924).

Feinblatt.⁷⁸ It is highly probable, therefore, that the opposite gland frequently, if not always, is somewhat functionally inadequate.⁷⁹ Removal of a functioning tumor under such circumstances throws a tremendous burden on the opposite gland, comparable to that which occurs in cases of adrenal apoplexy. The physiologic upheaval may be even more marked than that which occurs in crises of Addison's disease, because of the fact that the organism has had no opportunity to become adjusted to a low level of adrenal cortical function. The general plan of preoperative and postoperative treatment has been outlined by Walters and one of us (E. J. K.).⁵² It is based on the assumption that adrenal cortical insufficiency will occur after operation and should be prevented by treating the patient before the operation as if he had Addison's disease. If signs suggesting adrenal cortical insufficiency occur in spite of prophylactic treatment, vigorous therapy with adrenal cortical extract and a solution of sodium chloride is indicated. In this connection it is worth while to point out that although most, if not all, cortical extracts on the market vary in potency, they have one property in common; namely, enormous doses can be administered safely. (This statement does not apply to the synthetic compound desoxycorticosterone acetate.) A study of the reported cases in which death occurred after operation will convince any one that pusillanimous therapy is worthless under such circumstances.

A review of our own cases, as well as those which have been reported in the literature, indicates that imminent danger can be suspected after operation by a rapidly increasing temperature, a decreasing blood pressure, the clinical picture of "shock" and the chemical changes in the blood that accompany acute adrenal insufficiency. On theoretic grounds, the use of desoxycorticosterone acetate should constitute ideal preoperative and postoperative therapy. As yet no cases in which this substance has been employed for this particular purpose have been reported. We have used it, apparently with excellent results, in 1 instance in which a large malignant tumor of the adrenal cortex was successfully removed. This was not an ideal test case, because the only symptoms present were amenorrhea, hirsutism, an abdominal mass and a slight degree of rubicundity.

The treatment of hyperplasia of the adrenal cortex remains on a far less satisfactory basis than does that of adrenal cortical tumor. In some instances improvement has followed removal of one hypertrophic adrenal

78. Feinblatt, H. M.: Carcinoma of Cortex of Suprarenal Gland with Virilism, *Arch. Int. Med.* **38**:469-473 (Oct.) 1926.

79. We have gained the impression that this is especially true in cases in which there are marked metabolic abnormalities, as contrasted with cases in which there are virilizing phenomena.

gland or a portion of both hypertrophic adrenal glands, but usually the results have been relatively insignificant when compared with the phenomenal improvement which follows the removal of a tumor. When hyperplasia of the adrenal cortex is associated with a basophil adenoma of the pituitary body, irradiation of the latter at times has led to remarkable improvement, but on the whole the results of treatment of Cushing's disease have been most unhappy. Broster³² remains the leading exponent of unilateral adrenalectomy when hyperplasia is found in association with virilism.

DISEASES OF THE ADRENAL MEDULLA

Lesions of the adrenal medulla continue to be encountered far less frequently than do those of the cortex. Most common is primary malignant tumor of the adrenal medulla, which does not produce endocrine symptoms. The wide latitude of the histologic variations in such tumors has given rise to a distressing and confusing lack of uniformity in nomenclature. The tumor arises from sympathetic ganglion cells or their derivatives and, according to the degree of cellular differentiation present, generally is designated by such terms as sympathogonioma, sympathoblastoma, neuroblastoma, neurocytoma or glioma.

Malignant tumor of the adrenal medulla usually is encountered during childhood; reports of cases in which it has been observed in an adult are few. Fingerland,⁸⁰ however, encountered such a tumor in a 71 year old man.

The number of cases in the literature has grown steadily. Scott and associates⁸¹ in 1933 were able to collect 158 cases of the condition; Lewis and Geschichter⁸² a year later added 40 more, in 7 of which the lesions had originated outside the adrenal gland. Redman, Agerty, Barthmaier and Fisher⁸³ in 1938 reviewed reports of 113 cases which had been published since the appearance of the review by Scott and his co-workers.

The symptoms of the tumor in the majority of cases are produced by metastasis, although there have been occasional exceptions to this sequence. When metastasis to the orbit and skull occurs the tumor is customarily classified as the Hutchison type, whereas in cases of

80. Fingerland, A.: Sur un cas de paragangliome, *Bull. Assoc. franç. p. l'étude du cancer* **25**:334-349 (Feb.) 1936.

81. Scott, E.; Oliver, M. G., and Oliver, M. H.: Sympathetic Tumors of the Adrenal Medulla with Report of Four Cases, *Am. J. Cancer* **17**:396-417, 1933.

82. Lewis, D., and Geschichter, C. F.: Tumors of the Sympathetic Nervous System: Neuroblastoma, Paraganglioma, Ganglioneuroma, *Arch. Surg.* **28**:16-58 (Jan.) 1934.

83. Redman, J. L.; Agerty, H. A.; Barthmaier, O. F., and Fisher, H. R.: Adrenal Neuroblastoma: Report of a Case and Review of the Literature, *Am. J. Dis. Child.* **56**:1097-1112 (Dec.) 1938.

metastasis to the liver, with ascites, the tumor is known as the Pepper type. Division into these types is obviously arbitrary, and close inspection of reported cases indicates that many of the lesions have had features of both. Kato and Wachter⁸⁴ analyzed 179 such neoplasms, of which 76 were of the Hutchison type, 57 were of the Pepper type and 2 were of the mixed type. The remaining 44 were impossible to classify. In 93 cases the tumor occurred in boys, in 73 cases it occurred in girls and in 13 cases the sex was not stated. The average age of the patients suffering from tumor of the Hutchison type was 3.9 years, and the average age of those suffering from tumor of the Pepper type was 1.7 years.

In a number of instances bizarre hematologic changes have added confusion to the diagnosis. Von Albertini and Willi⁸⁵ reported a case in which a neuroblastoma of the right adrenal body of the Hutchison type remained undiagnosed during the life of the patient, a girl 2½ years old, for whom studies of the blood and bone marrow had suggested leukemia.

Treatment of such lesions has rather obviously been hopeless, and to date no record has been encountered of any case in which the patient has survived for any length of time. Surgical treatment in most instances has been out of the question because of the obvious presence of metastasis. Malisoff⁸⁶ encountered a case which constituted a remarkable exception: A girl 14 years old had a tumor weighing 2,435 Gm. which was removed from one adrenal body.

Lake and Ayers⁸⁷ reported the recovery of a girl 3½ years old after irradiation of a neuroblastoma of the right adrenal body. The period of observation had been short.

Medullary Hyperadrenalism.—Medullary hyperadrenalism resulting from a hyperfunctioning tumor of the adrenal medulla or an allied tumor of the chromaffin tissue has been recognized as a clinical and pathologic entity for a relatively short time. The tumor generally is termed pheochromocytoma or paraganglioma. Usually it is encapsulated and benign and possesses most of the histologic characteristics of adult chromaffin cells.

84. Kato, K., and Wachter, H. E.: Adrenal Sympathicoblastoma in Children, *J. Pediat.* **12**:449-462 (April) 1938.

85. von Albertini, A., and Willi, H.: Neuroblastoma Sympathicum der rechten Nebenniere mit Metastasierung nach dem Typhus Hutchison, *Ann. pædiat.* **152**: 129-159 (Dec.) 1938.

86. Malisoff, S.: Neuroblastoma of Adrenal Gland, *J. Urol.* **41**:296-302 (March) 1939.

87. Lake, W. F., and Ayers, A. J.: Renal and Perirenal Tumors in Children: Report of Two Cases, *South. M. J.* **31**:992-995 (Sept.) 1938.

Pheochromocytoma is an uncommon lesion. Brunschwig and Humphreys⁸⁸ reviewed the literature in 1939 and could find reports of only 103 cases of the neoplasm. Of these 103 tumors, 77 were unilateral, 13 were bilateral and 13 had occurred outside the adrenal body.

This tumor gives rise to a syndrome characterized by paroxysmal hypertension, vasomotor attacks, tachycardia, nausea, vomiting, tremor and, occasionally, glycosuria and elevation of the basal metabolic rate. The symptoms encountered obviously are those that might be expected to follow the sudden administration of an excess of epinephrine and may be exceedingly varied. Thorough summaries of the symptomatology have been published by Van Epps and associates⁸⁹ and Von Gärtner.⁹⁰

A number of instances have been reported in which hypertension was continuous.⁹¹ Sudden death, sometimes occurring during or after a minor surgical procedure, has been observed frequently.⁹² In most cases in which this syndrome has been encountered, analysis of the tumor for the presence of epinephrine has yielded enormous quantities of this substance.⁹³ Attempts to demonstrate excessive quantities of epinephrine

88. Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma, *J. A. M. A.* **115**:355-357 (Aug. 3) 1940.

89. Van Epps, E. F.; Hyndman, O. R., and Greene, J. A.: Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of the Adrenal Gland: Report of Two Cases, *Arch. Int. Med.* **65**:1123-1129 (June) 1940.

90. von Gärtner, W.: Das klinische Bild, insbesondere die Kreislaufstörungen bei Paragangliom der Nebenniere, *Ztschr. f. Kreislaufforsch.* **28**:82-90 (Feb.) 1936.

91. (a) Binger, M. W., and Craig, W. McK.: An Atypical Case of Hypertension with a Tumor of the Adrenal Gland, *Proc. Staff Meet., Mayo Clin.* **13**:17-20 (Jan. 12) 1938. (b) Edward, D. G. F.: Pheochromocytomata and Hypertension with Details of a Case, *J. Path. & Bact.* **45**:391-403 (Sept.) 1937. (c) Hegglin, R., and Nabholz, H.: Das Nebennieremarksyndrom: Zur Kasuistik der chromaffinen Geschwülste, *Ztschr. f. klin. Med.* **134**:161-195 (May) 1938. (d) Palmer, R. S., and Castleman, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension, *New England J. Med.* **219**:793-796 (Nov. 17) 1938. Van Epps, Hyndman and Greene.⁸⁹

92. Wells, A. H., and Boman, P. G.: The Clinical and Pathologic Identity of Pheochromocytoma: Report of a Case, *J. A. M. A.* **109**:1176-1180 (Oct. 9) 1937.

93. (a) Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla, *Surg., Gynec. & Obst.* **59**:9-24 (July) 1934. (b) von Brenner, F.; Konzett, H., and Nagl, F.: Ueber ein Phäochromozytom der Nebenniere, *München. med. Wchnschr.* **85**:914-916 (June 17) 1938. (c) Fein, M. J., and Carmann, F. F.: Medullary Carcinoma of the Suprarenal Gland (Pheochromocytoma), *Am. J. Cancer* **29**:301-306 (Feb.) 1937. (d) Fischer, H.: Bestimmung des Adrenalingehaltes des Nebennierentumors, *Ztschr. f. klin. Med.* **134**:184-195 (May) 1938. (e) Kelly, H. M.; Piper, M. C.; Wilder, R. M., and Walters, W.: Case of Paroxysmal Hypertension with Paraganglioma of the Right Suprarenal Gland, *Proc. Staff Meet., Mayo Clin.* **11**:

in the blood stream of patients during a hypertensive crisis have been fraught with great difficulties. Beers, King and Prinzmetal,⁹⁴ in 1937, using blood taken from a patient during such an attack, were able to demonstrate abnormal quantities of a pressor substance in the blood by perfusing it through the denervated ear of a rabbit. Moreover, they presented convincing evidence that this substance probably was epinephrine.

The diagnosis is associated with great difficulty, especially if the patient is not under observation during an attack, or if the hypertension is relatively continuous, rather than paroxysmal. Various authors have suggested a number of methods for the production of a hypertensive crisis, although the hazards incident to such procedures are sufficiently obvious. In some cases palpation of the renal region not only has precipitated a crisis but has helped to localize the tumor to one side.^{93g}

The treatment of such a tumor is surgical. Brunschwig and his associates⁸⁸ have emphasized the importance of prompt diagnosis and treatment because of the ever present menace of a fatal attack. Baumgarten and Cantor⁹⁵ reported a case in which death occurred from coronary occlusion. Cerebral and renal damage, as well as cardiac failure, in this patient could be attributed to repeated attacks of adrenal crises for nine years. Necropsy disclosed a small pheochromocytoma attached to the right kidney, several centimeters from the adrenal gland.

Successful removal of the tumor has been followed in almost every instance by cure. Surgical operation on these patients often has been extremely hazardous, death having occurred in a number of instances during the operation. MacKenzie and McEachern,^{93f} in 1938, could find reports of only 15 cases in which attempted surgical removal of a pheochromocytoma had been successful. A number of cases in which operation was successful have been published since. A detailed description of a successful operative technic was described by MacKenzie and McEachern.^{93f}

67-70 (Jan. 29) 1936. (f) MacKenzie, D. W., and McEachern, D.: Adrenal Pheochromocytoma, the Syndrome of Paroxysmal Hypertension: Report of a Case and Relief by Operation, *Tr. Am. A. Genito-Urin. Surgeons* **31**:127-154, 1938. (g) Strömbeck, J. P., and Hedberg, T. P.: Tumor of the Suprarenal Medulla Associated with Paroxysmal Hypertension, *Acta chir. Scandinav.* **82**: 177-189, 1939. (h) Estiu and Laborde.^{25d} (i) Edward.^{91b}

94. Beers, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of a Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crisis, *Ann. Surg.* **106**:85-91 (July) 1937.

95. Baumgarten, E. C., and Cantor, M. O.: Pheochromocytoma: Case Report, *Ann. Surg.* **111**:112-116 (Jan.) 1940.

A number of instances have been reported in which bilateral chromaffin tumors of the adrenal medulla have been associated with cutaneous neurofibromatosis. Rosenthal and Willis⁹⁶ in 1936 collected 6 cases of this curious syndrome from the literature and added a seventh. The cases discussed by these authors were not associated with the syndrome of medullary hyperadrenalism, but von Brenner and his associates^{93b} in 1938 reported the same association of symptoms in a patient who had paroxysmal hypertension. The tumor in this case was found to contain 1,200 mg. of epinephrine.

96. Rosenthal, D. B., and Willis, R. A.: The Association of Chromaffin Tumors with Neurofibromatosis, *J. Path. & Bact.* **42**:599-603 (May) 1936.

Correspondence

CHEMICAL FACTORS IN THE FORMATION OF GALLSTONES

To the Editor:—Some of the theories of gallstone formation are concerned with the maintenance of the solution of cholesterol in bile. About eleven years ago E. L. Walsh and A. C. Ivy (Observations on the Etiology of Gallstones, *Ann. Int. Med.* **4**:134 [Aug.] 1930) published results that seemed to indicate that the fatty acids or soaps in the bile exerted a more pronounced effect on cholesterol solubility than the bile acids. The former are in greater concentration in dog bile than in human bile, and this, according to Walsh and Ivy, accounts for the rarity of cholelithiasis in dogs and its frequency in human beings.

Later work by Dolkart, Jones and Brown from the same laboratory (Chemical Factors Concerned in the Formation of Gallstones, *ARCH. INT. MED.* **62**:618 [Oct.] 1938) supports this idea. The solubility of gallstone tablets was tested in a bile fraction that was obtained as follows: (Page 626 et seq.) An equal volume of alcohol was added to the bile and the filtrate was saponified with alkali. The nonsaponifiable insoluble fraction consisted of cholesterol to the extent of 80 per cent. The saponifiable or "fatty acid" fraction was used in the solubility experiments. As there was no mention made of separating the bile salts from the soaps, it appears that in every case this fraction contained both constituents. Yet these experiments led the authors to state that the solvent capacity of bile could be isolated in the fatty acid fraction. Later (page 630) they made the following statement: "In table 8 we attempted to correlate the relative activity of the various fatty acids as soaps on the basis of their molar concentration. . . . There was no correlation—indicating that the solvent activity was chiefly a chemical phenomenon." How this conclusion was obtained is not at all clear to us.

The average cholesterol content of human gallbladder bile is 0.3 per cent (Sobotka, H.: *Physiological Chemistry of the Bile*, Baltimore, Williams & Wilkins Company, 1937, p. 19), and according to Walsh and Ivy, dog gallbladder bile contains about one quarter of this amount. The ratio of soaps to cholesterol in dog bile is about twenty to one. While Dolkart, Jones and Brown maintained that sodium oleate in equal concentration dissolves four times more cholesterol than sodium cholate, it can be shown that the bile salts in dog bile are more than sufficient to dissolve the cholesterol contained therein. Let us assume that sodium taurocholate is present in dog bile in a concentration of 10 per cent. This is fair because sodium taurocholate is a relatively poor solvent for cholesterol (Bashour, J. T., and Bauman, L.: *The Solubility of Cholesterol in Bile Salt Solutions*, *J. Biol. Chem.* **121**:1, 1937), and 10 per cent is a conservative estimate for the concentration of bile acids in the gallbladder bile of dogs (Pickens, M.; Spanner, G. O., and Bauman, L.: *The Composition of Gall Stones and Their Solubility in Dog Bile*, *J. Biol. Chem.* **95**:505, 1932). Such a solution will dissolve almost twice the cholesterol that is present in the gallbladder of the dog.

Other statements contained in the article by Dolkart, Jones and Brown are equally open to question. For example, they spoke of the more frequent occurrence of gallstones in the human being, ox and hog than in the dog, cat, rabbit and sheep and intimated that the difference is due to a factor common to the group.

However, human gallstones consist almost entirely of cholesterol, ox gallstones of calcium bilirubinate and hog gallstones of lithocholate, that is, three substances with different chemical and physical properties. Should they not be considered individually rather than collectively?

The solubility values of pure cholesterol in pure bile salt solutions as determined by Bashour and Bauman are not in agreement with those of Dolkart, Jones and Brown. With compressed tablets of powdered gallstones Dolkart, Jones and Brown obtained an almost equal solubility in 5 per cent sodium cholate and sodium desoxycholate solution, whereas Bashour and Bauman obtained a 250 per cent greater solubility of pure cholesterol in the latter as compared with the former bile salt. This is in agreement with A. Rosin (Ueber die Lösung von Gallensteinen, *Ztschr. f. physiol. Chem.* **124**:282, 1923). Dolkart, Jones and Brown obtained the greatest cholesterol solubility in sodium cholate and progressively less in sodium taurocholate, sodium desoxycholate and sodium glycocholate. These results are also at variance with those of Bashour and Bauman. Our solubility values, using finely powdered, chemically pure substances, were reversibly tested and are to be considered as true solutions reproducible within the experimental error. At this point it may be well to emphasize that the immediate problem is the crystallization of cholesterol from bile and not the dissolution of concrements.

In a more recent article Dolkart, Lorenz, Jones and Brown (Relation of Fatty Acids and Bile Salts to the Formation of Gallstones, *ARCH. INT. MED.* **66**:1087 [Nov.] 1940) reported the study of the solubility of cholesterol tablets in solutions of the sodium salts of fatty and bile acids at a temperature of 70 C. The bearing of these data on conditions that obtain in the human gallbladder is not clear; it suggests that at body temperature the solvent effect of these salts is too slight to warrant a study of cholesterol solubility.

The solubility of cholesterol in 5 and 10 per cent soap solutions, which they reported, also has little bearing on conditions in the human gallbladder, since such concentrations, especially the higher, have rarely, if ever, been reported in human bile. The sudden drop in solvent capacity of bile when diluted by water can readily be explained by the known properties of bile salt solution, as indicated in the solubility studies of Bashour and Bauman.

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News and Comment

Salmon Memorial Lectures.—Dr. Robert D. Gillespie, psychiatric specialist of the British Royal Air Force, has been granted special leave of absence by the British government for the express purpose of delivering the Thomas William Salmon Memorial Lectures in the United States and Canada. These lectures, which have been titled "Psychoneuroses in Peace and War and the Future of Human Relationships," will be given, under the auspices of the Salmon Committee on Psychiatry and Mental Hygiene, in New York city on November 17 and 18, in Toronto, Canada, on November 19, in Chicago on November 21, in New Orleans on November 22, in Washington, D. C., on November 24 and 25, in San Francisco on November 27 and in Philadelphia on November 30. Dr. Gillespie will also make a report to members of the American medical profession and officers of the Morale Division of the United States Army and Navy in Hartford, Conn., on the psychologic effects of "Blitz" warfare on civilian and armed forces.

Book Reviews

Clinical Immunology, Biotherapy and Chemotherapy in the Diagnosis, Prevention and Treatment of Disease. By John A. Kolmer, M.D., Professor of Medicine, Temple University School of Medicine, and Louis Tuft, M.D., Assistant Professor of Medicine, Temple University School of Medicine. Price, \$10. Pp. XIII + 941, with 27 illustrations, including 11 color plates. Philadelphia: W. B. Saunders Company, 1941.

This book is well printed on good paper and is clearly illustrated. It is a comprehensive volume of 36 chapters divided into two distinct parts. The first part takes up about a third of the entire book and deals with the general aspects of infection, immunity and chemotherapy. The second, and longer, part is clinical in nature and discusses the practical application of immunity and chemotherapy to the prevention and treatment of disease. This is a bare outline of the skeleton of the volume.

Each chapter is well and clearly written in a style that any student or practitioner will appreciate. The sentences are terse and to the point. The subdivisions of each chapter are clearly marked off, so that one can easily find just what one is looking for. Outlines of diagnostic surveys or summaries of diseases are incorporated in an ingenious tabular form which willy-nilly catches the reader's eye and demands notice. The color plates showing the result of vaccination, cutaneous tests or such procedures are satisfyingly graphic. Best of all, each chapter ends with a brief summary and a carefully selected bibliography germane to the matter under consideration.

On the whole, this book has all the earmarks of a successful medical text. Countless students and physicians will procure it, studying it and underlining their favorite parts with the same meticulous care that its authors displayed in writing it.

Objective and Experimental Psychiatry. By D. Ewen Cameron, M.D. Second edition. Price, \$3.75. Pp. 390. New York: The MacMillan Company, 1941.

The author observes the unity of the organism with its environment and the necessity of studying the reactions of the whole organism, but expresses the belief that "habitually coordinated activities exist within the human organism which have as good a claim to be studied as wholes as does the whole represented by the organism itself." He scales the functions of the organism on the basis of the speed and extent to which they promote adaptation. At the top of the scale are learning and remembering. Lower level functions include autonomic and metabolic activities, and lowest in the scale are those functions which take many generations to develop. Tension, emotion and mood are well considered from the standpoint that "tension is a state of psychobiological preparedness." The latest work on sleep, convulsive disorders, metabolic activities, drugs, endocrine glands and heredity is all considered in its relation to upper level functions. A large amount of pertinent psychologic and physiologic research is critically examined. The book needs a summarizing chapter.

Lymphatics, Lymph and Lymphoid Tissue: Their Physiological and Clinical Significance. By Cecil Kent Drinker and Joseph Mendel Yoffey. Price, \$4. Pp. 406, with 50 illustrations and 44 tables. Cambridge, Mass.: Harvard University Press, 1941.

This monograph deals with the physiologic and clinical significance of the lymphatic apparatus in mammals. It is a revision and extension of a previous monograph by Drinker and Field. The anatomic and physiologic organization

of the lymphatic system, the permeability of blood capillaries and its relation to lymph formation, the functional significance of lymphoid tissue and the composition and flow of lymph are dealt with extensively and authoritatively. The necessity of a knowledge of the physiology of the lymphatic system to an understanding of numerous clinical problems, such as edema, inflammation and surgical shock, is clearly pointed out. The clinician will find much of value and the biologic investigator a wealth of stimulating ideas in this clearly written and well documented treatise.

Diseases of the Nails. By V. Pardo-Castello, M.D., Assistant Professor of Dermatology and Syphilology, University of Habana. With a foreword by Howard Fox, M.D., Professor of Dermatology and Syphilology, New York University College of Medicine. Second Edition. Price, \$3.50. Pp. XXI + 193, with 98 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This edition is practically a reprint of the first one, with 4 more illustrations, a few more pages and an up-to-date bibliography. The *ARCHIVES* (60:1114 [Dec.] 1937) and *The Journal of the American Medical Association* (108:232-233 [Jan. 16] 1937) each reviewed the original volume, favorably calling it, in effect, a useful monograph on an unusual subject, practical, short, plainly written and well illustrated. Those who do not own the first edition will be glad to know of the second. It continues to be an excellent small book to have on hand for reference.

Synopsis of Applied Pathological Chemistry. By Jerome E. Andes and A. G. Eaton. Price, \$4. Pp. 428, with 23 illustrations and 35 tables. St. Louis: C. V. Mosby Company, 1941.

Ever since Vierordt published his famous "Tabellen" many years ago the need of compendiums of medical data has been recognized. No one can carry in his head all the values for physiologic, anatomic and chemical constants useful in clinical medicine; no one can keep in mind the details of the many biologic tests in current use. Synopses like this book, which in addition to technical details have some discussion of interpretation, are always useful, but their very briefness and hence dogmatic tendency may be criticized. The present volume contains a mine of useful material and could well have a place on the physician's shelf, or even in his bag.

Cardiac Clinica. By Fredrick A. Willius. Price, \$4. Pp. 276, with 35 illustrations. St. Louis: C. V. Mosby Company, 1941.

These are the days of superspecialization, and almost every internist wants to be a cardiologist. Cardiology is a clearcut definite subject and one which involves attractive methods of precision, such as electrocardiography. As a result there has literally been a flood of monographs during the past four years on various aspects of heart disease. Dr. Willius uses the case history method to present vividly the outstanding features of cardiac disorders. A case or two each night should make good and useful bedtime reading for the tired practitioner. The volume is attractively got up and is full of excellent photographs and charts.

Handbook of Communicable Diseases. By Franklin H. Top and collaborators. Price, \$7.50. Pp. 682, with 73 illustrations and 10 color plates. St. Louis: C. V. Mosby Company, 1941.

This excellent book calls to mind that there are few satisfactory treatises on communicable diseases in English. The authors' experience with purely clinical problems as well as with those concerning public health and isolation hospitals results in a happy combination for the student of the subject. The discussions

are well written and include recent advances in knowledge; the illustrations (many of them in color) are excellent, and the chapters on the technic of dealing with communicable disease are especially valuable.

Microbes Which Help to Destroy Us. By Paul W. Allen, D. Frank Holtman and Louise Allen McBee. Price, \$3.50. Pp. 540, with 105 illustrations and 13 color plates. St. Louis: C. V. Mosby Company, 1941.

Here in semipopular style but with accuracy of fact are told the stories of the principal infectious diseases. The authors use the historical approach, and the biographic material about the great pioneers in bacteriology is pleasantly presented. This book makes ideal vacation reading for the medical student or physician, or even for the intelligent layman.

Hypertonie und Sklerose der Blutstrombahn. By Prof. Dr. Med. Fritz Lange. Price, 18 marks. Pp. 224. Leipzig: Theodor Steinkopff, 1941.

In this the fifth in a series of monographs on the circulation, the author discusses the clinical aspects, pathology, etiology, genesis and treatment of hypertension and vascular sclerosis.

Although the book makes interesting reading, the reviewer can hardly recommend it to any one desiring a thorough and detailed insight into this subject.

CORRECTION

In the article by Oliver P. Jones, Ph.D., entitled "Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis: I. Quantitative Effect of Diets Containing Ventriculin" (*Arch. Int. Med.* **68**:476 [Sept.] 1941), the last three lines in the paragraph preceding "Observations" on page 484 should have been incorporated in reference 47, at the bottom of the page.

ELLIPTIC ERYTHROCYTES IN MAN

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OMAHA

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In recent years attention has been directed to the fact that the red cells of an apparently healthy person are not necessarily round but may be distinctly elliptic or even sausage shaped. This condition has been recognized as a congenital anomaly, frequently called "ovalocytosis" in spite of the fact that the red cells are not strictly oval. This paper describes the incidence in 3 interrelated families of pure German extraction of 86 members with large numbers of such cells. This is the largest group for which this condition has been reported. In addition, we present features of the anomaly not previously recorded.

REVIEW OF THE LITERATURE

Because reports of this condition have appeared in many languages and are not universally accessible, it seems desirable to present here a fairly complete review of the literature.

To Dresbach¹ goes the credit for reporting the first case of the anomaly. A mulatto medical student discovered during a class exercise that 90 per cent of his red cells were elliptic rather than round. They ranged in width from 3.9 to 4.8 microns and in length from 8.5 to 10.7 microns. Smears were shown to several pathologists, including Arneith, Ehrlich, Ewald and Ewing, who suggested that the anomaly might be of congenital or developmental origin. A brother of the student had only round cells; so the hereditary nature of the anomaly could not be proved. Because the student died shortly afterward, Flint² suggested

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1. Dresbach, M.: Elliptical Human Red Corpuscles, *Science* 19:469-470 (March 18) 1904.

2. Flint, A.: Elliptical Human Erythrocytes, *Science* 19:796 (May 20) 1904.

that pernicious anemia or purpura might have caused the deformity of the cells, and death as well, which statement Dresbach³ later refuted. This may not have been the first observation of the anomaly, since Ewald wrote Dresbach that a similar observation had been made at Königsburg, Germany, twenty or thirty years earlier. Lambrecht⁴ reported that also in Königsburg, in 1860, Goltz had observed elliptocytosis in a woman. These 2 reports might have concerned the same person.

In 1914, Bishop⁵ gave support to the concept of the congenital nature of the anomaly by reporting its occurrence in a man and his sister. Their father, another sister and her 2 children had normal cells. In both of the first-named persons the hemoglobin concentration was 100 per cent or above and the red cell count was 5,000,000 or more. The reticulocyte count and the result of fragility tests were normal.

The next case, that of a Negro, was reported by Sydenstricker,⁶ in 1923. The patient had a mild degree of anemia, with 90 to 95 per cent of his red cells elliptic. In the same year, Huck and Bigelow⁷ studied a case of the anomaly in much detail. The blood of a female medical student was observed daily for three weeks, but the number of deformed cells remained unchanged. Several times the student acted as a donor of blood for transfusions, and in 1 recipient no elliptic cells were found after two months, although there is no record of observations in the interim. The authors concluded that the shape was inherent in the cells themselves and was probably due to an anomaly of the blood-forming organs and not to outside influences.

The report by Lawrence,⁸ in 1927, of a person whose blood contained 5 to 10 per cent sickle-shaped or elliptic red cells and whose brother, sister and niece had similar blood pictures, is open to question as presenting true examples of the anomaly, because of the scarcity of cells. He also reported 5 other instances in a series of 102 normal adults in which photomicrographs of the blood showed only rare elliptic cells and concluded that in these 5 cases the persons probably should not be

3. Dresbach, M.: Elliptical Human Erythrocytes, *Science* **21**:473 (March 24) 1905.

4. Lambrecht, K.: Die Elliptocytose (Ovalocytose) und ihre klinische Bedeutung, *Ergebn. d. inn. Med. u. Kinderh.* **55**:295-319, 1938.

5. Bishop, F. W.: Elliptical Human Erythrocytes, *Arch. Int. Med.* **14**:388-390 (Sept.) 1914.

6. Sydenstricker, V. P.: Elliptic Human Erythrocytes, *J. A. M. A.* **81**:113-114 (July 14) 1923.

7. Huck, J. G., and Bigelow, R. M.: Poikilocytes in Otherwise Normal Blood (Elliptical Human Erythrocytes), *Bull. Johns Hopkins Hosp.* **34**:390-393 (Nov.) 1923.

8. Lawrence, J. S.: Elliptical and Sickle-Shaped Erythrocytes in Circulating Blood of White Persons, *J. Clin. Investigation* **5**:31-49 (Dec.) 1927.

considered as elliptic cell bearers. He expressed the belief that sickle cell anemia and elliptocytosis were related phenomena.

A new idea was introduced in 1928 by Günther,⁹ who, by painstaking measurement of a large number of cells, separated human red cells into four classes on the basis of shape: class I, round; class II, roundish; class III, elliptic, and class IV, narrow elliptic. Of these, classes III and IV should not comprise more than 12 per cent, and class IV alone more than 0.4 per cent of the total number of red cells. He concluded that the elliptic form was the primary form of the vertebrate animal, inherent in the architectural structure of the cell. He reported 3 cases of tower skull, in 1 of which elliptic cells were present, and 2 additional isolated cases of the anomaly.

A report by van den Bergh,¹⁰ in the same year, of a young girl whose father and 2 sisters also possessed elliptic red cells further pointed to the congenital nature of the anomaly. This concept was somewhat refuted by Bernhardt¹¹ after he observed a patient whose blood contained a large number of elliptic red cells, who had a moderate anemia, but whose father, mother, 2 sisters and their children had only round red cells. A few months later van den Bergh¹² reported another case of the anomaly, in which symptoms of hemolytic icterus were not accompanied by increased fragility. After splenectomy was performed, the icterus disappeared but the elliptic red cells remained.

In 1929, Hunter and Adams¹³ definitely established the hereditary nature of the anomaly by their study of three generations of a Dutch-American family. The blood of 5 members of this family contained many elliptic red cells, while that of 7 more showed only a few such cells. A few years later, Hunter¹⁴ added to this family tree 5 more American members whose blood contained a few elliptic red cells, and van den Bergh¹⁵ added 4 more to the Dutch branch of this same family.

9. Günther, H.: Die klinische Bedeutung der Ellipsenformen der Erythrozyten, *Deutsches Arch. f. klin. Med.* **162**:215-230, 1928.

10. van den Bergh, A. A. H.: Elliptische rote Blutkörperchen, *Arch. f. Verdauungskr.* **43**:65-69 (March) 1928.

11. Bernhardt, H.: Ovalozytose der Erythrozyten als Anomalie, *Deutsche med. Wchnschr.* **7**:756-757 (April 15) 1928.

12. van den Bergh, A. A. H.: Elliptische rote Blutkörperchen, Addendum, *Deutsche med. Wchnschr.* **54**:1244 (July 27) 1928.

13. Hunter, W. C., and Adams, R. B.: Hematologic Study of Three Generations of White Family Showing Elliptical Erythrocytes, *Ann. Int. Med.* **2**: 1162-1174 (May) 1929.

14. Hunter, W. C.: Further Study of White Family Showing Elliptical Erythrocytes, *Ann. Int. Med.* **6**:775-781 (Dec.) 1932.

15. van den Bergh, A. A. H.: A propos des hématies elliptiques (l'ovalocytose), *Rev. belge d. sc. méd.* **3**:683-688 (June-July) 1931.

One more isolated case was reported in 1931 by Roth and Jung,¹⁶ that of a 30 year old woman with icterus but with normal fragility of the red cells. Two sisters had round red cells. Two doubtful cases of the anomaly, with associated anemia and only a few elliptic red cells, and 1 apparently authentic case, with many elliptic red cells, were described by Lawrence,¹⁷ who questioned whether, because of the abnormal type of cell, anemia might develop more readily in persons with elliptic red cells than in those with normal red cells.

One of the most comprehensive studies of the nature of the condition was made by Terry, Hollingsworth and Eugenio,¹⁸ in 1932. They studied before death and at autopsy 2 unrelated patients who had died of disease. The elliptic cells were heavier, settled more rapidly and were less fragile than the round cells. They showed also that the cells were elliptic in the circulating blood and that their shape was not merely the result of artificial conditions after removal from the body.

Any doubt of the hereditary nature of the anomaly was dispelled by Cheney,¹⁹ in the same year, by a study of 3 generations of a family in which 13 members had elliptocytosis and a fourteenth had only a few elliptic red cells. He established the transmission of elliptic red cells as a mendelian dominant and saw no sound basis for assuming any relation between the anomaly and anemia.

In 1933, Rotter²⁰ reported 9 cases of the anomaly in 3 generations of a white family in Costa Rica, although his record of the family tree was not complete. From Germany, in the same year, Grzegorzewski²¹ reported 14 cases in 3 generations, with enough information to assume the carriers in another generation of ancestors. In 6 of these cases icterus and increased fragility of the red cells were also present, although Grzegorzewski stated that the anomaly had no relation to disease. Another large family was investigated, also in 1933, by Rosenow,²² who found 12 members in 4 generations with numerous elliptic red cells.

16. Roth, O., and Jung, E.: Zur Kenntnis der Ovalozytose, *Folia haemat.* **44**:549-554 (July) 1931.

17. Lawrence, J. S.: Human Elliptical Erythrocytes, *Am. J. M. Sc.* **181**: 240-245 (Feb.) 1931.

18. Terry, M. C.; Hollingsworth, E. W., and Eugenio, V.: Elliptical Human Erythrocytes: Report of Two Cases, *Arch. Path.* **13**:193-206 (Feb.) 1932; *M. Bull. Vet. Admin.* **9**:7-17 (July) 1932.

19. Cheney, G.: Elliptic Human Erythrocytes, *J. A. M. A.* **98**:878-881 (March 12) 1932.

20. Rotter, W.: Elliptische rote Blutkörperchen als familiäre vererbare Anomalie, *Klin. Wchnschr.* **12**:1777 (Nov. 11) 1933.

21. Grzegorzewski, H.: Ueber familiäres vorkommen elliptische Erythrozyten beim Menschen, *Folia haemat.* **50**:260-277, 1933.

22. Rosenow: Elliptische rote Blutkörperchen als familiäre vererbare Anomalie, *Klin. Wchnschr.* **12**:481-482 (March 25) 1933.

Members of one branch of the family had a hereditary anomaly of the teeth, a defect of the superior lateral incisors, present in three generations. Rosenow found also that with venous stasis the percentage of elliptic red cells both in venous and in capillary blood increased. From Poland, Finkel²³ reported 2 instances of the anomaly in persons who also had anemia with sickle cells, accompanying massive infestation with lice. He expressed the belief that the two anomalies were identical, the different manifestations constituting only variations of the physico-pathologic state which he called "dolichocythemia." He mentioned that the same blood picture, without an associated infestation with lice, occurred in children of these 2 persons although the number of children was not recorded.

An idea of the frequency with which the anomaly occurs was given in 1934 by McCarty,²⁴ who discovered 4 instances in the routine examination of 10,000 persons. Seven additional cases were found among the relatives of the 4 affected persons, all Negroes. McCarty found, too, that if the cells were washed with lecithin they all became round, while washing with cholesterol had no effect. In her series, the number of elliptic cells tended to decrease with succeeding generations, as a blended mendelian characteristic would do if the original trait was a sport. Pollock and Dameshek,²⁵ in the same year, confused the anomaly with the sickling trait by reporting the occurrence both of elliptic and of sickle-shaped cells in the blood of members of a Jewish family. The authors considered the two conditions different stages of the same phenomenon.

In 1935, Stephens and Tatelbaum²⁶ observed relative microcytosis and polycythemia accompanying elliptocytosis and an average red cell count of 6,470,000 in 8 members of one family. They considered it probable that in affected persons the potentiality for deformity was possessed by all mature erythrocytes, and perhaps to a lesser degree by the reticulocytes. That the change in shape occurred during or after the reticulocyte stage was shown by Schartum-Hansen.²⁷ He observed the anomaly in an anemic woman submitting to liver therapy, under which condition the reticulocyte response could be studied. A son of

23. Finkel, A.: Ovalocytemia and Drepanocytemia in People of the White Race, *Polska gaz. lek.* **12**:562 (July 23) 1933.

24. McCarty, S. H.: Elliptical Red Blood Cells in Man: Report of Eleven Cases, *J. Lab. & Clin. Med.* **19**:612-621 (March) 1934.

25. Pollock, L. H., and Dameshek, W.: Elongation of Red Blood Cells in Jewish Family, *Am. J. M. Sc.* **188**:822-834 (Dec.) 1934.

26. Stephens, D. J., and Tatelbaum, A. J.: Elliptical Human Erythrocytes: Observations of Size, Volume and Hemoglobin Content, *J. Lab. & Clin. Med.* **20**: 375-383 (Jan.) 1935.

27. Schartum-Hansen, H.: Die Genese der Ovalozyten, *Acta med. Scandinav.* **86**:348-360, 1935.

the woman also possessed the same type of red cell, but in fewer numbers. He expressed the belief that it was improbable that the mere 169 elliptic reticulocytes observed in the peripheral blood could represent the preliminary stage of 36,112 elliptic erythrocytes, while 790 round reticulocytes were the precursors of only 2,929 mature round erythrocytes. In his opinion, the elliptic cell was the end, or destructive, stage of all red corpuscles, the cause of the increased number of which in these 2 instances might be endocrine.

Babudieri²⁸ observed the anomaly in a mother and her 2 daughters with hypochromic anemia and in 2 members of another family. He thought that anemia might coexist with elliptocytosis but was not necessarily an accompaniment. In the blood of clinically healthy persons, the condition constituted a unique index of a particular constitutional state of the hemopoietic system, which in other persons might manifest itself in clinical anemia or even in pernicious anemia, depending on the intervention of various factors. In the same year Schemensky²⁹ reported 2 cases of the anomaly. He expressed the belief that the carriers of elliptic erythrocytes behaved normally and that the elliptic cell was not to be brought into causal relation to disease.

In 1937 reports of the condition became more numerous, and in general larger families were encountered. Janoušek, Štancl and Vacková³⁰ reported it in a Czech woman and her son and suggested that some of the abnormality of shape might be an artefact or the result of the Hamburg phenomenon. Horwitz³¹ reported 1 case of the anomaly in the same year, and Ljudvinovsky,³² from Russia, recorded 4 isolated cases, in which the available relatives all had only round red cells. Strauss and Daland³³ examined the blood of 36 members of a Russian-Jewish family, none of whom was known to have had jaundice or anemia. The mother, 3 of her 8 daughters and 6 of their 11 children showed elliptic red cells. Of these 10 persons, 27.7 to 61.0 per cent of the red cells showed a difference between the long and the short diameter of 2.5

28. Babudieri, B.: Alcuni nuovi casi di ellipsocitemia, *Haematologica* **17**: 73-76, 1936; Due casi di ellipsocitemia (ovalocitemia) Prima segnalazione in Italia, *ibid.* **17**:135-140, 1936.

29. Schemensky, W.: Die Ovalozytose, eine vererbbare Anomalie der Erythrocyten, *Med. Welt* **10**:1686-1687 (Nov. 21) 1936.

30. Janoušek, S.; Štancl, O., and Vacková, K.: Oval Erythrocytes in Man, *Casop. lék. česk.* **76**:872-876 (June 7) 1937.

31. Horwitz, S.: Thrombophlebitische Splenomegalie und Ovalozytose, *Harefuah* **12**:iii (May) 1937.

32. Ljudvinovsky, R. J.: On the Subject of Ovalocytosis, *Terap. arch.* **14**: 721-727, 1936.

33. Strauss, M. B., and Daland, G. A.: Hereditary Ovalocytosis (Human Elliptical Erythrocytes): Observations on Ten Cases in One Family, *New England J. Med.* **217**:100-103 (July 15) 1937.

microns or more, while in 5 persons with normal erythrocytes only 3.2 to 8.2 per cent of the cells showed that difference. The authors stated that the anomaly was transmitted as a mendelian dominant unit character. From Java, Kouwenaar³⁴ reported 14 cases in a Javanese family, the first to be reported from Asia. Bertelsen³⁵ observed 10 cases in a family near Copenhagen, Denmark, in 4 of which the liver and spleen were enlarged and in 2 of which there was icterus. He questioned whether the chronic infection which was present in these cases might cause the anemia or whether the elliptic cells with the accompanying anemia might be a predisposing factor in infection. In Downey's "Handbook of Hematology," Mason³⁶ has a section on ovalocytosis. He described 5 additional cases, in 1 of which there was accompanying anemia for which no cause was apparent. This association and the occurrence of similar cases in the literature led him to advance the theory that anemia might develop on, and was in some way related to, a vulnerable hemopoietic system, of which ovalocytosis was the direct expression. In this respect, the phenomenon might be analogous to that of sickle cell anemia and hemolytic icterus, in which the trait is more frequent than the disease.

In the same year, Lambrecht⁴ reported 16 cases in 3 generations of 3 families living in Frankfurt-am-Main, Germany. He was the first to distinguish definitely between the normal person and the bearer of the anomaly by assuming that elliptocytosis existed if the sum of the cells characteristic of Günther's classes III and IV exceeded 25 per cent of the total number of red cells. He expressed the belief that this division was important for the recognition of what he called "latent carriers," persons having less than 25 per cent of elliptic red cells. In 2 of the families studied, anemia and jaundice with decreased resistance of the red cells were present, which led Lambrecht to assume a correlation between the anomaly of shape and the clinical signs. In his cases the presence of increased hemopoiesis led him to separate the condition into active, compensated and latent forms. Steinbrinck and Hahnelt³⁷ reported, also in 1938, 4 cases in 1 family and 2 cases in unrelated persons. They suggested the condition was a manifestation of a sort of atavism. Gigon,³⁸ also from Germany, observed 6 cases in three generations of a family. From America came two reports in addition to that

34. Kouwenaar, W.: Form of Erythrocytes with Special Consideration of Elliptocytosis, *Geneesk. tijdschr. v. Nederl.-Indië* **78**:827-840 (April 12) 1938.

35. Bertelsen, A.: Case of Familial Elliptocytosis, *Ugesk. f. læger* **100**:136-140 (Feb. 10) 1938.

36. Mason, V. R.: Ovalocytosis, in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 3, pp. 2351-2360.

37. Steinbrinck, W., and Hahnelt: Ueber familiäre Ovalocytose, *Deutsche med. Wchnschr.* **54**:784-785 (May 27) 1938.

38. Gigon: Ovalozytose, *München. med. Wchnschr.* **85**:157 (Jan. 28) 1938.

of Mason. Florman and Wintrobe³⁹ recorded 11 cases in 3 families in which at least 40 per cent of the red cells were elliptic and 10 per cent were rod shaped. No member of any family, 2 of which were Negro and 1 of which was white, had anemia. They considered that the elliptic erythrocytes could be present in man as a familial condition and also in cases of a macrocytic type of anemia. Miller and Lucas⁴⁰ observed 9 cases in 4 generations of a family in Louisville, Ky. They suggested the existence of a secondary intraerythrocyte susceptibility to a primary extraerythrocyte influence, either or both of which might be congenital.

During 1939 all but 1 of the reports came from Europe. The largest family studied was reported by Lieberherr⁴¹; 22 instances of the anomaly were found among the 63 members whose blood was examined. In all cases microcytosis was present but not considered essential. Lieberherr expressed the belief that no definite relation existed between elliptic cells and the state of health and that any association with anemia was entirely accidental. Söderström⁴² reported 3 isolated cases, in 2 of which the volume index was low, but no signs of hemolytic icterus were present. Vischer⁴³ found 12 persons with the anomaly in 3 generations of a Swiss family, with sufficient evidence to postulate the existence of 2 more in a fourth generation. He asserted that accurate measurement of the cells by Günther's method was unnecessary for recognition of the anomaly. In the cases which he reported, although the subjects were healthy, with no definite icterus or anemia, there was evidence of increased hemopoiesis in the bone marrow, borne out also by high reticulocyte counts. Transfusion experiments⁴⁴ showed also that the elliptic red cells had a life span of only twelve or thirteen days, shorter than that of normal erythrocytes. He concluded that there existed a predisposition to anemia, which was usually entirely compensated. Unless the compensation was broken by infection or increased activity of the spleen, the only hematologic evidence of the condition, other than the elliptic cells themselves, was increased erythropoiesis. One of the most comprehensive articles on elliptocytosis was that of Leitner⁴⁵ in which

39. Florman, A. L., and Wintrobe, M. W.: Human Elliptical Red Corpuscles, *Bull. Johns Hopkins Hosp.* **63**:200-220 (Oct.) 1938.

40. Miller, J. K., and Lucas, M. A.: Elliptical Erythrocytes in Human Blood, *Am. J. Clin. Path.* **8**:391-397 (July) 1938.

41. Lieberherr, W.: Ueber Ovalocytose, *Helvet. med. acta* **5**:589-596 (Nov.) 1938.

42. Söderström, N.: Ovalocytosis, *Nord. med. tidskr.* **16**:1996-2000 (Dec. 17) 1938.

43. Vischer, A.: Untersuchungen über Ovalozytose, *Ztschr. f. klin. Med.* **135**:123-132, 1938.

44. Vischer, A.: Ueber die Lebensdauer der Erythrocyten. Beobachtungen bei Transfusionen mit Ovalozytenblut, *Ztschr. f. klin. Med.* **135**:133-136, 1938.

45. Leitner, S. J.: Die familiäre Elliptocytose als vererbare Anomalie der Erythrocyten, *Deutsches Arch. f. klin. Med.* **183**:607-646, 1939.

he reported the cases of 4 full carriers and 2 part carriers. He also cited Schulten's⁴⁶ report of a family with 2 definite carriers of the anomaly and 2 whose blood contained only a few elliptic cells and expressed the belief that part carriers are important in the detection of family relationships. He asserted that anemia was not an essential accompaniment of elliptocytosis and that in most cases it was not demonstrable. According to his viewpoint, if families with normal red cells were as thoroughly investigated hematologically as those with elliptic red cells, just as many instances of unexplained anemia might be revealed. He observed slight microcytosis, with normal erythropoiesis, in the cases he reported and suggested that any increased hemolysis reported by other authors must be due to the fact that the elliptic cells were older and fragmented more readily than did the younger round cells. To him the anomaly was of important genetic significance, since it represented the smallest cell carrier of definite hereditary characteristics, whether arising as a result of mutation or as a direct peculiarity inherited through uncounted generations, whereby primary elliptic cells in the ancestors must be assumed. Giffin and Watkins⁴⁷ reported 8 cases of the anomaly at the Mayo Clinic, in 5 of which the elliptocytosis was regarded as accidental and not contributing to the patient's illness. In 3 cases in 1 family, it was associated with typical features of hemolytic icterus, although 1 member showed no clinical symptoms. In the 2 showing clinical symptoms of hemolytic icterus, elliptocytosis remained after splenectomy.

Reports which probably should not be included in a review of the literature of elliptic red cells are those by Fanconi⁴⁸ and Introzzi.⁴⁹ The former reported a case, observed through fourteen years, of primary hemolytic hyperchromic elliptocytanemia with icterus and anemia and a large number of elliptic cells, which responded poorly to splenectomy. He asserted that this condition was a disease entity which should be separated from familial hemolytic icterus and elliptocytosis. Introzzi discussed the case of a patient with hypochromic anemia, elliptocytosis, poikilocytosis, increased hemoglobin exchange and slight icterus. This patient, also, responded poorly to splenectomy. A similar blood pic-

46. Schulten, H.: *Die Sternalpunktion als diagnostische Methode*, Leipzig, Georg Thieme, 1936; cited by Leitner.⁴⁵

47. Giffin, H. Z., and Watkins, C. H.: *Ovalcytosis with Features of Hemolytic Icterus*, *Tr. A. Am. Physicians* **54**:355-358, 1939.

48. Fanconi, G.: *Die verschiedenen Formen der primären hämolytischen Anämien; die hyperchrome Elliptozytenanämie und ihre Differentialdiagnose gegenüber der Perniziosa und der Kugelzellanämie*, *Arch. f. Kinderh.* **117**:1-32 1939.

49. Introzzi, P.: *Anemia ipocromica splenomegalica emolitica con ovalocitosi (ellitticitosi), poichilocitosi ed aumento della resistenza osmotica der globuli rossi*, *Splenectomia*, *Haematologica* **16**:525-579, 1935.

ture was found in a sister and a cousin of the patient. Introzzi expressed the belief that the elliptocytosis occurring in these persons was the same as that occurring in healthy ones.

The total number of cases of definite elliptocytosis reported in this summary is 246, occurring in 64 families. In 31 cases, representing 7 additional families, it is questionable, because of the small number of elliptic cells observed, whether the persons concerned were true carriers of the anomaly.

EXPERIMENTAL PROCEDURE

In this study, the first case of the anomaly was discovered accidentally during an examination of the blood of D. B., who came to the dispensary of the University of Nebraska Hospital, Omaha, in October 1936, complaining of an axillary lymphadenopathy. At that time his hemoglobin concentration was 12.3 Gm. per hundred cubic centimeters, his red cell count was 4,900,000 and approximately 92 per cent of his red cells were either elliptic or rod shaped. His mother and 1 brother had similar blood pictures, while those of his father and sister showed only round red cells. Only round cells had been found in sections of tissue taken at autopsy of a male twin of the brother, who had died at the hospital several years before. The mother had 9 siblings and her father had 11, all of whom were living and were examined in this study. During the course of the investigation, 3 spouses were found who showed the same anomaly, and an attempt was made to test the various members of the families of 2 of them. In all, more than 600 persons were tested in these 3 families and in others distantly related by blood, in an attempt to discover a relationship between them or a common ancestor of the three. With the help of the Akademische Auslandsstelle and the Gesundheitsamt, blood was examined from 43 persons in Germany in the locality from which the ancestors of the 3 families emigrated in 1869. Records of family lineage were studied there also.

In the beginning, only dry smears and moist preparations of blood were made. No. 0 cover glasses were used, and the preparations were sealed with petrolatum. For those persons whose blood contained elliptic red cells, red cell counts, hemoglobin estimations, reticulocyte counts and blood group determinations were made with standard technics. Later, for a linkage study, the blood group was determined for all persons whose blood was examined for elliptic red cells. A more detailed examination of 14 persons with elliptic cells included complete blood counts and determination of the icterus index, van den Bergh reaction, the red cell fragility, the hematocrit value and the cholesterol content of the blood. (Three and a half years later the blood of 1 of these persons was reexamined.) In addition, the red blood cells of several persons were measured with the euscope, according to the method of Sauder and Toomey,⁵⁰ and the individual red cells in a selected field of a moist preparation were measured daily for five days to determine the constancy of shape of the cells.¹ Daily counts of the number of elliptic cells were made for 1 person for three weeks, as well as repeated estimations of the urobilinogen in the urine; the latter were made because of the increased red cell turnover reported by Lambrecht⁴ and by Vischer.⁴³ Cord blood was obtained in 3 cases at the time of delivery. Counts of the elliptic cells

50. Sauder, H. R., and Toomey, J. A.: Rapid Measurement of Red Cells, *Am. J. Dis. Child.* **41**:823-828 (April) 1931.

in each instance were made on the moist preparations on the day on which the specimens were obtained and in an area in which the film was thin, rouleaux were absent and the cells were not distorted. Cells which showed a distinct difference between the long and the short diameter were considered elliptic. At least 600 cells were counted in each instance. These preparations were observed at intervals for several weeks. In addition, blood from 450 healthy medical students and nurses was examined, as well as blood smears from 1,000 patients consecutively admitted to the hospital, a fairly accurate cross section of the population of the state in general. This examination was considered necessary because of the large number of instances of the anomaly found during the course of the investigation. To ascertain whether the anomaly was inherent in the plasma or in the cells themselves, washed and unwashed suspensions of the cells were mixed with homologous normal serum and plasma, and washed and unwashed normal cells were added to the serum and plasma of elliptic cell carriers of the same blood group. An attempt was made also to substantiate the statement of Terry and associates¹⁸ that the elliptic cells are heavier and less fragile than are normal red cells.

RESULTS

Definition of an Elliptic Cell Carrier.—Among our first decisions was the number of elliptic cells required to warrant designating a person as an elliptic cell carrier. The incidence of elliptic red cells in the blood of the 450 students and nurses is indicated in the following tabulation:

Percentage of Students and Nurses	Percentage of Elliptic Red Cells
58	1 or less
37	2 to 5
4	5 to 10
1	10 to 15

Of the 1,000 patients, 2 whose blood contained 29 and 38 per cent, respectively, of elliptic red cells had definite anemia and 1 whose blood had 22 per cent of such cells had no anemia. According to Günther,⁹ in a normal person the sum of the red cells of classes III and IV should not exceed 12 per cent, or in rare instances 22 per cent. Florman and Wintrobe³⁹ restricted the anomaly to those persons with more than 40 per cent elliptic and 10 per cent rod-shaped cells, while Lambrecht⁴ placed the dividing line at 25 per cent. Since no member of a family in this series in which there were no elliptic cell carriers had more than 15 per cent elliptic red cells unless anemia was present, 25 per cent was arbitrarily chosen as a conservative dividing line. Rarely were elliptic cell counts in the zone between 10 and 25 per cent encountered, while 40 per cent was the lowest number found in any definite case in our series and it was observed in a member of a fourth family who had married into one of the 3 families reported. We realize that estimations made in this manner are not as accurate as actual measurements by Günther's method or by Price-Jones curves, but we

found it possible with practice to check repeated estimations closely, so the procedure was continued. Lambrecht,⁴ Leitner⁴⁵ and Schulten⁴⁶ have designated as part carriers persons with only a few elliptic red cells. We feel that the designation is not justified, because in our experience a true bearer of the anomaly will have more than 25 per cent of his cells definitely elliptic, while normal members of families in which elliptic cells occur have less than 10 per cent such cells, as do normal persons in general. The fact that the red cells may be caused to round up by irregularities of the slide or cover glass, as well as any pressure applied to the latter, may account for the cases in which only a few elliptic cells were reported.

Genetic Observations.—The genealogic charts of the three families studied are shown in figures 1, 2 and 3. Individual families which

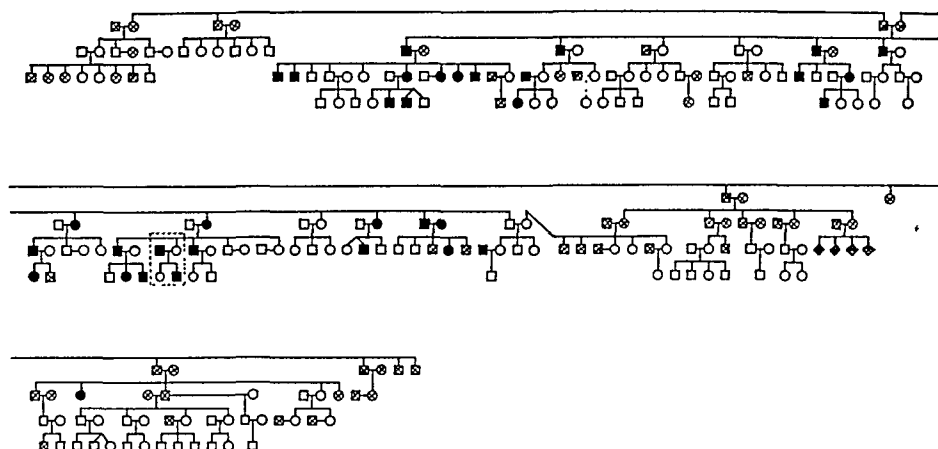


Fig. 1.—The incidence of elliptocytosis in family T. The following symbols bear the same significance for family T., family A (fig. 2) and family W (fig. 3): white square, a male with normal red cells; white circle, a female with normal red cells; black square, a male with elliptic red cells; black circle, a female with elliptic cells; square enclosing a cross, a male whose blood has not been examined for elliptic red cells; circle enclosing a cross, a female whose blood has not been examined for elliptic red cells, and diamond enclosing a cross, a person of unknown sex whose blood has not been examined for elliptic red cells. In figures 1, 2 and 3 a dotted line surrounding an individual family group indicates that the group appears also on one of the other two family charts.

belonged to two genealogic charts were counted with the family to which the elliptic cell parent belonged. On the chart of the family of the nonelliptic cell parent such an individual family is indicated by a dotted line. In the case of the family with 2 elliptic cell parents, the father and daughter are counted with his family. In all, 86 members of the three families showed elliptical cells. In the case of family T., the presence of the trait in 1 descendant of a brother of the mother (long dead) suggests that she, rather than the father, was the carrier

of the trait. In a personal communication Dr. Karl Nieberding, of Oldenburg, Germany, tells of the discovery of other members with elliptic cells in the same branch of family T. there, after one of us (H. W.) returned to America, but the war has prevented a detailed report of them. Twenty-eight instances of the anomaly occurred in family A., 28 in family W. and 30 in family T. (the original family).

In this series there were definitely more males with the anomaly than without it, as well as more affected males than females, especially

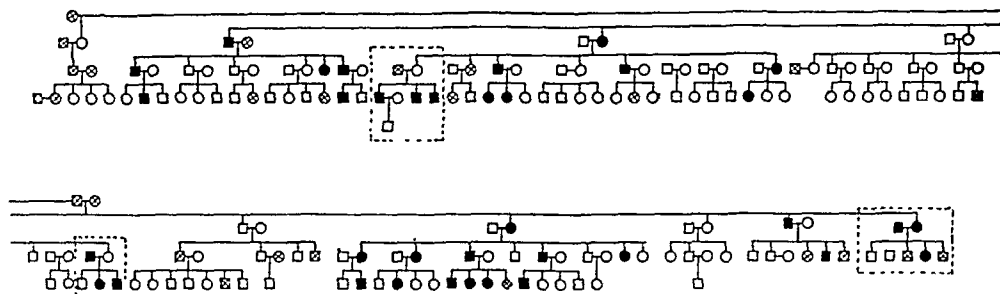


Fig. 2.—The incidence of elliptocytosis in family A.

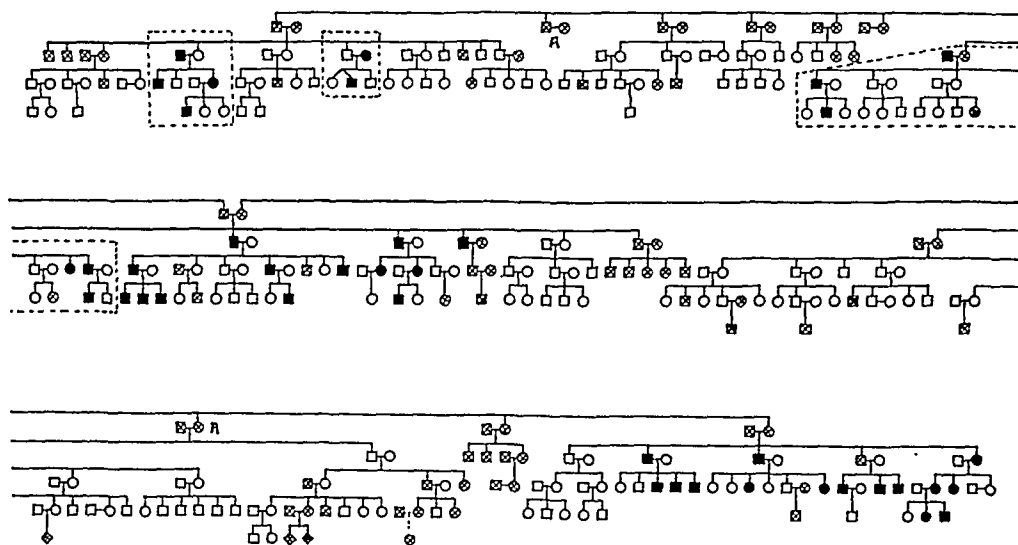


Fig. 3.—The incidence of elliptocytosis in family W.

when the father was the affected parent. When the total cases reported in the literature were considered, this apparent difference in sex incidence disappeared. This series of cases shows features not found in those previously reported. In 1 instance, both parents exhibited the anomaly. From this mating were born 2 sons with round cells, 2 sons who had died before this study was begun and 1 daughter with elliptic cells and, in addition, spherocytes and other evidences of hemolytic icterus, such as splenomegaly, markedly increased fragility of the red cells, high reticulocyte count and jaundice. Two pairs of twins are represented. Of a pair of fraternal twins, 1 had elliptic cells and the other had not.

It is difficult to say whether the other pair were identical, since 1 died at the age of 11 months. The living twin showed the anomaly, while sections of tissue made at autopsy of the other showed only round cells. That elliptic cells may be readily found in tissue sections from elliptic cell bearers was shown by Terry and associates.¹⁸

Hematologic Studies.—When sealed moist preparations of whole blood were allowed to stand in the laboratory, in the refrigerator or in the incubator (37.5 C.), the cells tended to round up, as shown in table 1, which gives measurements of the individual cells in a single high power field one, three and five days after the preparation was made. This rounding-up process was shown both by an increase in the shortest

TABLE 1.—*The Changes (in Microns) in the Diameters of Cells in Moist Preparations, Measured by Means of a Euscope*

Cell No.	First Day	Third Day	Fifth Day
1.....	5.68 × 11.45	5.83 × 9.58	6.04 × 8.12
2.....	5.00 × 11.45	5.83 × 10.20	6.25 × 9.14
3.....	6.04 × 9.37	6.66 × 6.87	6.66 × 6.87
4.....	5.31 × 10.20	5.62 × 9.14	5.83 × 8.95
5.....	3.33 × 8.54	5.31 × 8.12	5.83 × 8.12
6.....	5.41 × 10.00	5.62 × 9.14	6.25 × 8.12
7.....	6.45 × 11.04	6.45 × 10.64	6.45 × 9.14
8.....	5.83 × 10.41	6.04 × 9.79	6.25 × 8.95
9.....	4.79 × 12.29	5.00 × 10.00	5.00 × 9.58
10.....	5.41 × 9.79	5.62 × 9.58	5.62 × 9.37
11.....	3.33 × 8.70	5.00 × 7.70	5.41 × 7.29
12.....	6.25 × 10.00	6.87 × 7.91	6.87 × 7.03
13.....	5.00 × 10.41	5.41 × 8.12	5.62 × 7.29
14.....	4.37 × 9.58	4.79 × 8.71	5.41 × 7.29
15.....	4.16 × 10.41	4.16 × 9.58	4.16 × 9.37
16.....	5.31 × 11.25	5.31 × 10.64	5.31 × 8.95

diameter and by a decrease in the longest diameter of the individual cells. Preparations kept for three to four weeks showed few elliptic cells. At the end of four weeks, unidentified large brown crystals resembling a sheaf of wheat appeared regularly in mounts of elliptic cells as the cells began to disappear and rarely in the preparations of round cells. The significance of this phenomenon was not determined.

To establish the constancy of shape of the cells of any given person, counts were made daily on 1 subject during the course of a three and a half week stay in the hospital. The percentage of elliptic cells varied from 88 to 92, while that of the sausage-shaped cells ranged between 17 and 25. This constancy agrees with that reported by Huck and Bigelow⁷ and by Leitner,⁴⁵ while Pollock and Dameshek²⁵ found diurnal variation. On one day, one of four preparations had twice as many sausage forms as the other three mounts made at the same time. Since the technic of washing the slides and cover slips and making the preparations was identical, as nearly as one could tell, we were at a

loss to explain this difference. It does suggest, however, that there may be some as yet unidentified outside or inside influence capable of altering the shape of the red cell which might be a factor in this anomaly.

Preparations of these persons' cells, washed or unwashed, mixed with normal serum or plasma, however, showed no alteration in the shape of the cells for several days, although after three weeks all but a few cells had become round, even though well preserved. Since this happened even in moist preparations of whole blood of the elliptic cell carriers, no significance was attached to the fact that the cells became round in the foreign plasma also. Practically all observers have noted that there is no alteration in shape either of elliptic cells suspended in normal plasma or of normal red cells in plasma of an elliptic cell carrier. This has been interpreted by most authors to mean that the elliptic shape is inherent in the structure of the cell itself.

Sternal punctures were made in 2 cases. In each, approximately 80 per cent of the non-nucleated red cells were elliptic, although all of the nucleated erythrocytes were round or nearly so. There was no evidence of increased erythropoiesis.

Reticulocyte counts were slightly elevated, the percentage of these cells ranging from 1.6 to 13. In general, the greater number of the cells showing basophilia were round, in the proportion of 2 to 10 round reticulocytes to 1 elliptic cell, with 2 exceptions. F. M. (family T.) had 2.2 per cent round reticulocytes and 3.6 per cent elliptic cells, while E. A. (family T.) had 4 and 9.6 per cent, respectively. The fact that the majority of the reticulocytes, as well as the normoblasts in the bone marrow, are round suggests that the elliptic shape is assumed during or after the reticulocyte stage, as has been well demonstrated by Schartum-Hansen.²⁷ To reconcile the fact that the cells assume the elliptic shape after leaving the bone marrow and coming in contact with the plasma, while normal cells are uninfluenced by the same plasma, Miller and Lucas⁴⁰ have suggested a secondary intraerythrocyte susceptibility to a primary extraerythrocyte influence, either or both of which might be inherited. On the other hand, both round and elliptic cells are found in the plasma of the same person, which speaks against any action of the plasma alone.

We were unable to substantiate the assertion by Terry and his associates¹⁸ that the elliptic red cells settled more readily, were heavier and were less fragile than normal red cells, possibly because in the blood of persons in this series of cases the round cells were too few to allow accurate separation from the elliptic ones.

It is in respect to a possible relationship of the anomaly to anemia that considerable controversy exists. In our cases the subjects were singularly free from any type of anemia, and the individual family members were unusually healthy and long lived. In only 1 instance was definite anemia present. A child, E. A. (table 2), both of whose

TABLE 2.—Results of Laboratory Tests

Patient	Age, Yr.	Degree of Elliptocytosis, Per. centage	Red Cell Count	Hemo- globin, Gm. per 100 Cc.	Reticulocytes, Percentage		Mean Cor- puscular Volume, Cubic Microns	Mean Cor- puscular Hemo- globin	Mean Cor- puscular Hemo- globin Concen- tration	Icterus Index	Van den Bergh Reaction		Red Cell Fragility		Choles- terol, Mg. per 100 Cc.
					Round	Elliptic					Direct	Indirect, Mg. per 100 Cc.	Beginning Hemolysis	Complete	
F. A.	71	83	5,400,000	16.2	2.0	1.0	85.5	31.5	37.1	6	Negative	0.3	0.46%	0.30% NaCl	218
L. A.	69	83	5,200,000	16.5	90.0	33.6	37.0	6	Negative	0.3	0.41%	0.30% NaCl	230
O. A.	52	87	5,700,000	17.8	2.7	0.6	92.0	33.5	36.1	7	Negative	0.2	0.48%	0.34% NaCl	221
E. A.	49	95	4,500,000	13.1	2.3	1.3	89.0	31.4	35.2	6	Negative	0.1	0.50%	0.34% NaCl	201
W. A.	43	82	5,100,000	15.5	87.0	32.0	35.2	0.16%	0.35% NaCl	215
H. C.	32	73	5,100,000	14.4	2.2	0.7	86.0	36.0	35.3	3	Negative	0.1	0.44%	0.32% NaCl	218
P. A.	40	91	4,800,000	15.7	1.4	0.4	98.0	34.5	33.2	6	Negative	0.2	0.48%	0.32% NaCl	176
H. A.	28	80	5,400,000	16.5	1.3	0.2	95.0	32.0	31.0	6	Negative	0.2	0.48%	0.34% NaCl	165
M. A.	27	96	5,000,000	15.2	88.0	32.5	37.0	8	Negative	0.1	0.16%	0.32% NaCl	228
M. B.*	36	92	4,800,000	13.6	2.6	1.2	85.0	33.0	38.8	5	Negative	0.2	0.16%	0.30% NaCl	181
C. B.	28	96	5,000,000	13.4	79.4	26.4	33.2	10	Negative	0.5	0.50%	0.31% NaCl	...
N. M.	16	93	4,900,000	14.9	2.0	0.2	85.5	32.8	38.3	9	Negative	0.1	0.44%	0.32% NaCl	160
E. A.	12	81	4,200,000	10.9	4.0	9.0	75.5	28.0	36.0	20	Negative	1.6	0.85%	0.20% NaCl	140
D. B.	9	92	4,900,000	12.3	3.0	0.6	74.0	27.5	35.0	..	Negative	0.1	0.18%	0.30% NaCl	167
M. B.*	40	90	4,100,000	11.6	90.1	23.2	31.3	7	Negative	0.2	0.10%	0.30% NaCl	207

* The same patient. The second tests were made three and a half years after the first ones.

parents had elliptic cells in large numbers, had a red cell count of 4,200,000 and a hemoglobin concentration of 9.8 Gm. per hundred cubic centimeters. In addition, she had a positive indirect van den Bergh reaction, markedly increased red cell fragility, a high reticulocyte count and spherocytosis, as well as an enlarged spleen, an icteric tint to the skin and a history of previous hemolytic crises typical of those associated with familial hemolytic icterus. In figure 4, a photomicrograph of her blood can be compared with one of blood taken from an elliptic cell carrier. The fragility of the red cells of the mother and father was normal, as were the icterus index, the van den Bergh reaction and the reticulocyte count; no definite spherocytes were seen. Neither had any knowledge of having had jaundice or of its occurrence in any member of the immediate families, besides the daughter. Two living children have always been healthy, but they refused to have samples of blood taken for determining the icterus index and for making fragility tests. One other child died suddenly in infancy, and another died of peritonitis after an appendectomy. Splenomegaly and jaundice have been reported in elliptic cell bearers by Bernhardt,¹¹ Introzzi,⁴⁹ van den Bergh,¹² Grzegorzewski,²¹ and Bertelsen³⁵; jaundice alone, by Roth and Jung,¹⁶ Lambrecht⁴ and Fanconi,⁴⁸ and increased red cell fragility, by Ljudvinovsky,³² Pollock and Dameshek,²⁵ Vischer⁴³ and Babudieri,²⁸ in addition to van den Bergh, Roth and Jung and Grzegorzewski. Except for the increased fragility, the blood picture for this child is similar to that reported by Introzzi⁴⁹ as one of hypochromic anemia, with elliptocytosis and poikilocytosis, which he considered a distinct disease entity, separate both from elliptocytosis and from familial hemolytic icterus. The definite occurrence in E. A.'s blood both of elliptic cells and of spherocytes suggests the simultaneous occurrence of the two red cell anomalies, in spite of the absence of spherocytes in the blood of either parent. The fact that both father and mother are elliptic cell bearers, the only case of this on record, may have some bearing.

Additional evidence that spherocytosis and elliptocytosis can coexist is found in the cases reported by Introzzi⁴⁹ and Fanconi⁴⁸; while possibly the condition was not true elliptocytosis in either case, both spherocytes and elliptical cells did exist simultaneously. Dr. John C. Sharpe,⁵¹ of Omaha, had 1 case in which both types of cells occurred, together with typical clinical and laboratory signs of familial hemolytic icterus. After splenectomy, both types of cell persisted, although clinical symptoms of hemolytic icterus disappeared. Van den Bergh reported an instance in which signs of hemolytic icterus, with the exception of increased red cell fragility, were present. These signs disappeared after splenectomy, while the elliptic cells persisted. Two patients of Giffin and Watkins⁴⁷ showed both clinical symptoms of true familial hemo-

51. Sharpe, J. C.: Personal communication to the authors.

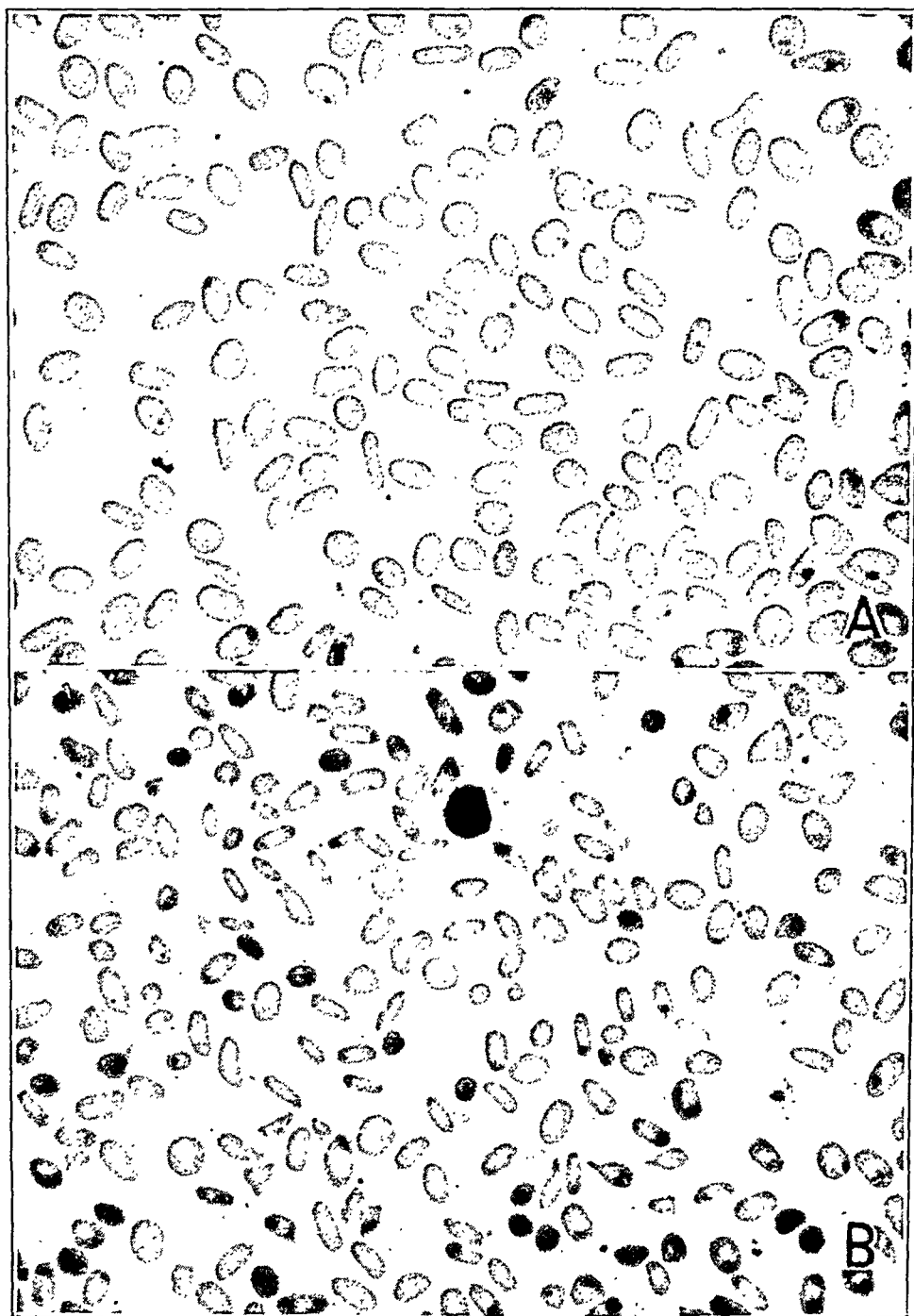


Fig. 4.—*A*, elliptic red cells in the blood of a healthy carrier. *B*, elliptic red cells and spherocytes in the blood of patient E. A.

lytic icterus and elliptic cells in large numbers; the elliptic cells persisted after splenectomy. Because the term hemolytic anemia covers such a variety of conditions resulting from such different causes, with only increased hemolysis in common, it does not seem unreasonable that atypical cases of a hemolytic type of anemia might occur in an elliptic cell family, as well as in a family with only round red cells. These cases suggest, however, that true hemolytic icterus of familial type with spherocytes, increased fragility of the red cells and other laboratory and clinical signs can occur in elliptic cell bearers. If a definite relation could be established between true hemolytic icterus with spherocytosis and elliptocytosis with spherocytosis, it would be a distinct hematologic advance.

With 3 exceptions, 2 of them in children, the mean corpuscular volume, the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration of the persons examined were within normal limits. In the 3 exceptions, there was slight microcytosis. This has been reported by Lieberherr,⁴¹ Stephens and Tatelbaum²⁶ and Leitner,⁴⁵ but the majority of investigators found a normal cell volume in spite of the great variation in shape of the red cells.

In the rest of the series the occurrence of red cell counts and hemoglobin estimations which were normal or above led us to think that slight polycythemia might accompany this elliptocytosis, as was found by Stephens and Tatelbaum.²⁶ Round cell members of the same families, however, showed similar polycythemia. In spite of the 1 subject with anemia (E. A.), we feel that this large series of unusually healthy and long-lived carriers should speak strongly against any obligatory relationship between the anomaly and anemia. This conclusion is in agreement with those of Gigon,³⁸ Rosenow,²² Florman and Wintrobe,³⁹ Vischer,⁴³ Leitner,⁴⁵ Schemensky,²⁹ Lieberherr,⁴¹ Miller and Lucas⁴⁰ and Strauss and Daland.³³

On the other hand, Mason³⁶ points to the cases of elliptocytosis in the literature in which associated anemia is unexplained (Hunter and Adams,¹³ van den Bergh¹² and Lawrence⁵²) and reports another as evidence that anemia developed on, and was in some way related to, a vulnerable hemopoietic system of which elliptocytosis was a direct expression. Vischer⁴³ expressed the belief that the more rapid hemoglobin turnover was evidence of a predisposition to anemia, and Lambrecht⁴ asserted that anemia was evidence of decompensation accompanying the increased hemolysis which he observed in the cases he reported. The blood of 1 member of our series, M. B. (family T.), which was examined many times during three weeks, showed no evidence of increased hemolysis detectable by repeated determinations of

52. Lawrence (footnotes 8 and 17).

the urobilinogen in the urine, the icterus index or the van den Bergh reaction. During this period, she underwent a serious gynecologic operation which might have precipitated a break in the compensation had increased hemolysis been a factor. In addition, bone marrow studies made on this subject during this time showed normal erythropoiesis. There may be considerable truth in the statement by Leitner⁴⁵ that if families with normal red cells were investigated hematologically as thoroughly as families in which elliptocytosis occurs, just as many cases of unexplained anemia might be detected as have been reported in connection with that anomaly.

In analogy to the red cell anomalies of spherocytosis and drepanocytosis, in which the trait is much more common than the accompanying disease, it seems logical that a disease entity might accompany this red cell anomaly also. This supposition is made even more logical by the fact that in certain forms of anemia, especially pernicious anemia⁹ and other types of macrocytic anemia,³⁹ as well as that accompanying lymphatic leukemia, a relatively large number of the red cells are elliptic, while spherocytes and sickle cells occur only as an anomaly. In addition, a few such cells are found in the blood of almost all normal persons. The presence of this type of cell both in a normal person and in association with a definite pathologic condition of the hemopoietic system suggests that some variation of the same force or factor is responsible in both cases. However, the various types of anemia which have been reported in elliptic cell bearers have been too diverse to constitute a basis for any distinct clinical entity comparable to familial hemolytic icterus or sickle cell anemia, and the incidence has been too inconstant to indicate an essential relationship. It seems that our series of cases should add further evidence that the anomaly has no definite relation to disease.

The cause of the anomaly is entirely unknown. It has been shown conclusively that the change to the elliptic shape takes place during or after the reticulocyte stage and is inherent in the structure of the cell itself. For that reason, it has been suggested by Scharf-Hansen²⁷ and Leitner⁴⁵ that the elliptic cell is an old form of erythrocyte—an end stage, as it were—since a few such cells are present in the blood of all normal persons. Leitner expressed the belief that the shorter life span of the elliptic cells, as indicated by the transfusion experiments of Vischer,⁴⁴ was due to the fact that the elliptic cells were older, and consequently were closer to the end of their life span.

With the exception of the mammals, the erythrocytes of vertebrate animals are elliptic and nucleated. Of the mammals, the Camelidae alone have elliptic, non-nucleated cells. The change from nucleated, elliptic cells to non-nucleated cells is demonstrated in two families of salamanders, represented by *Batrachoseps attenuates* and *Aneides*

lugubris⁵³ which are identical, except the structure of the gills and red blood cells. In the former, which has but rudimentary gills, the nuclei from the red cells have been lost, possibly to increase the oxygen-carrying capacity of the cell to compensate for the lack of oxygenating surface in the gills. The change from elliptic to round cell may have resulted in a manner equally logical. In fact, Terry and his associates¹⁸ suggested that elliptocytosis might furnish a link between the marine vertebrates and man. According to them, the elliptic shape might have been assumed from some earlier necessity, theoretically, a less constant plasma, while the disk might have developed later as an adaptation to conditions, such as a fully developed species-specific plasma, in which such degree of rigidity of form was no longer necessary or advantageous. Such an adaptation of cells and plasma in progress and not yet complete can be seen in the blood groups in which the agglutinins are not present in the full amount at birth.⁵⁴ That a certain adaptation of a similar type occurs in this condition is exemplified by the case reported by Hunter,¹⁴ and by 1 case of this series, in which the elliptic cells in the blood from the umbilical cord were few but increased markedly in the circulating blood after birth. In the former case, they increased to 41.4 per cent oval and 1.6 per cent elongated cells three months after birth. In the latter, 11 per cent of the cells were elliptic at birth, but had increased to 80 per cent four months later.

This observation adds certain weight to the view of Schartum-Hansen²⁷ and of Leitner⁴⁵ that the elliptic cell is an older form, since the blood of a newborn infant also shows a higher number of young red cells than does that of an adult, with 1 to 24 normoblasts per 100 leukocytes and a percentage of reticulocytes as high as 20.⁵⁵ Within a week or two after birth, these values reach adult levels. In the case reported by Hunter, the elliptic cells increased markedly during the first week of life. This change also might indicate some process of adaptation of cells to plasma, in progress but not complete, as suggested before.

Various causes other than age have been suggested, such as faulty erythropoiesis, defective bone marrow, a mutation and some form of atavism, but no definite one has been established.

Recent reports indicate that the anomaly is more common than hitherto considered. The incidence has been given as 0.04 to 3 per cent, with the lower figure probably the more correct.⁴⁰ During the four

53. Emmel, V. E.: Hematological and Respiratory Conditions in the Larval Stages of the Lungless Amphibians *Batrachoseps Attenuates* and *Aneides Lugubris*, *Anat. Rec.* **21**:56, 1921.

54. Wiener, A. S.: *Blood Groups and Blood Transfusion*, Springfield, Ill., Charles C. Thomas, Publisher, 1935, pp. 15-19.

55. Wollstein, M., in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 2, pp. 930-932.

years in which this study has been in progress only 2 additional cases have been found in the course of approximately 7,000 examinations, although in a large number of smears as many as 10 per cent of the red cells were elliptic. Florman and Wintrobe³⁹ reported that in 89 per cent of persons without anemia and in 98 per cent of persons with anemia, elliptic cells were found. One to 15 per cent of the cells of the former were elliptic, while in 12 per cent of those with anemia more than 25 per cent of the cells were elliptic. The anomaly has been reported for almost every race except Chinese, Japanese and Hindu, with the largest number of cases reported from among the German people.

According to Strauss and Daland,³³ elliptocytosis is transmitted as a simple mendelian dominant unit character, to which statement practically all observers have agreed. The individual family in this series in which both parents and 1 child show the anomaly and 2 children do not definitely proves that the anomaly could not be a recessive characteristic, if there was any need for such proof. In only 1 instance, reported by Bernhardt,¹¹ has the anomaly been observed in the offspring of parents both of whom had only round red cells, an occurrence which might be possible if it arose as a mutation.

The medicolegal significance has been suggested by Miller and Lucas⁴⁰ and should be emphasized. Although rare, the occurrence of elliptocytosis might aid in the identification both of person and of paternity. This possibility was realized in the case of another family studied by two of the authors (H. W. and P. B.) but not reported in this series. In addition, the ease of recognition of the anomaly makes it valuable in linkage studies of various inherited characteristics.

Several questions remain to be settled. The relation of the anomaly to anemia has not been definitely proved, although this large series of cases should add support to the theory that the two conditions are not definitely correlated. There is a question whether there might not be two entities, simple elliptocytosis and a condition in which elliptic cells, as well as poikilocytes and even spherocytes, coexist with a definite degree of anemia. Whether any abnormal characteristics accompany the condition has not been settled entirely. Tower skull⁹ and anomalies of the teeth and the jaws⁵⁶ have been reported. In this series no such anomalies were found. Its relation to blood groups has not been settled. The etiology is unknown. Another question to be settled is the significance of so-called part carriers, mentioned by Lambrecht, Leitner and Schulten, as well as the importance of the few elliptic cells constantly present in the blood of members of nonelliptic cell families and the larger number of such cells found in persons with anemia.

56. Finkel.²³ Lambrecht.⁴

SUMMARY

Eighty-six new cases of elliptocytosis in 3 large families of German extraction are reported. In this series, the trait was more frequent in males than in females.

The occurrence of this condition in 2 pairs of twins, is reported; 1 member of each pair had elliptic red cells, while the other had round ones.

One family is reported in which both the father and the mother had elliptic cells in large numbers.

Laboratory data are given for 14 cases, as well as experimental data to show some of the characteristics of elliptic cells.

In 1 case there was laboratory and clinical evidence of both elliptocytosis and spherocytosis.

The fact that all other members were free from anemia, unusually healthy and long lived, lends support to the opinion that the anomaly has no definite relation to disease.

EFFICACY OF INTRAVENOUS SODIUM BICARBONATE THERAPY IN THE TREATMENT OF DIABETIC KETOSIS

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Intravenous administration of sodium bicarbonate was first used in the treatment of diabetic ketosis in 1886¹; although it has been a recognized procedure in most clinics for the ensuing fifty-five years, there is even yet little agreement as to its efficacy. Of the various reasons for this discrepancy, one is most apparent. So many different prognostic and therapeutic factors influence the outcome of the disease that evaluation of any single procedure, such as administration of sodium bicarbonate, is rendered difficult. The purpose of this paper is twofold, to discuss the effect of intravenous administration of sodium bicarbonate on blood sugar, carbon dioxide-combining power and ketones in the blood and urine during the treatment of diabetic ketosis and to report the effect of sodium bicarbonate therapy on coma mortality in 154 cases of ketosis, which were classified in five groups according to severity of the condition.

Not all of the chemical changes associated with diabetic ketosis can be explained in detail, but the reasons for the increased number of ketones in the blood and the lowered level of bicarbonate in the plasma are fairly well understood. Carbohydrate metabolism is interfered with during the development of diabetic ketosis, so abnormally large quantities of fat are broken down. Ketones, the intermediary products of fat combustion, occur in excess. Some are exhaled through the lungs or are oxidized directly in the tissues, but the greater number appear in

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1. Wolpe, S.: Untersuchungen über die Oxybuttersäure des diabetischen Harns, Thesis, Königsberg, Leipzig, J. B. Hirschfeld, 1886.

the urine. Many ketones are organic acids as well, and before excretion can take place the sodium salts of the various acids are formed. The sodium ions for this reaction are drawn from the alkali reserve or the total base content of the blood. Since the effect of the sodium ions as potential alkali is lost once the salts are excreted in the urine and since ordinarily no steps are taken to replenish the reserves of sodium during the development of ketosis, the alkali reserve is soon exhausted and acidosis results.

The carbon dioxide-combining power is a measure only of the changes in the electrolytes in the blood, or the degree of acidosis. On the other hand, determination of the ketones in the blood measures directly the disturbance of fat metabolism and indirectly the disturbance of carbohydrate metabolism. Since ketones are formed only from fats and since fats are burned abnormally, because in the presence of uncontrolled diabetes the body is unable to utilize carbohydrates properly, measurement of the blood ketones affords a reliable index of the severity of the underlying metabolic changes.

The problem of death from diabetic ketosis is not solved by correcting the blood sugar, blood ketones and carbon dioxide-combining power. Many patients with ketosis have died, though they were chemically cured. The mental state of the patient and the duration of mental symptoms have been found to be more closely related to the eventual outcome than have other factors.² The amount of treatment, the age of the patient, the presence of circulatory collapse and infection all play a part in recovery. It was thought wise, therefore, to take these factors into consideration and then compare the mortality for patients treated with sodium bicarbonate with that for patients, not so treated, to determine whether practical benefit results from its administration.

METHOD

In 12 unselected cases of severe diabetic ketosis the usual forms of therapy (parenteral administration of physiologic solution of sodium chloride, insulin and dextrose) were started. Fifteen hundred cubic centimeters of physiologic solution of sodium chloride was given on admission to the hospital and repeated as necessary. Insulin was given hypodermically at the rate of 40 to 50 units an hour, until the sugar in the blood and urine approached normal limits. From then on the hourly dose of insulin was reduced according to the individual needs of the patient. Dextrose was administered when the level of sugar in the blood approached normal if acetone still persisted in the urine.

Samples of blood were drawn and oxalated on admission and every three hours thereafter until the ninth hour. Determinations of dextrose, carbon dioxide-combining power and ketones were made on each sample. In 4 cases the total output of urine was collected for three hour periods and preserved for determination of ketones. The dextrose in the blood was measured by the method of Somogyi,

2. Owens, L. B., and Rockwern, S.: Prognosis of Diabetic Coma: Basic Importance of Mental State, *Am. J. M. Sc.* **198**:252-260, 1939.

Shaffer and Hartman.³ The carbon dioxide-combining power of the serum was determined according to the method of Peters and Van Slyke,⁴ and the ketones in the blood and urine, by the Van Slyke method, with Denige's reagent.⁵

In 9 of the 12 cases of diabetic ketosis intravenous administration of a 5 per cent solution of sodium bicarbonate was started either immediately or three hours after admission. The remaining 3 cases, in which no sodium bicarbonate was given, were used as controls. Pertinent data for these 12 cases are set forth in figures 1 and 2.

The mortality rate was also studied in 154 consecutive cases of diabetic patients who were admitted to the Cincinnati General Hospital for ketosis. Since the terms "ketosis" and "acidosis" are used rather loosely in many clinics, certain criteria were set up as a basis of selection of cases for this study. The minimum requirements were evidence of uncontrolled diabetes severe enough to require hospital treatment, presence of sugar and acetone in the urine, initial blood sugar over 200 mg. per hundred cubic centimeters and carbon dioxide-combining power under 30 volumes per cent. In most cases either drowsiness or unconsciousness was

Relation Between Therapy with Intravenous Administration of Sodium Bicarbonate and Mortality in One Hundred and Fifty-Four Cases of Diabetic Ketosis

Intensity of Ketosis	47 Cases in Which 10 Gm. (or More) of Sodium Bicarbonate Was Administered				107 Control Cases in Which No Sodium Bicarbonate Was Administered			
	Recovery		Death		Recovery		Death	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Extremely mild.....	1	100	0	0	8	100	0	0
Mild.....	4	100	0	0	17	95	1	5
Moderately severe.....	9	63	6	40	21	67	11	33
Severe.....	7	54	6	46	17	53	15	47
Extremely severe.....	1	8	13	92	1	6	16	94

also present, and in many cases nausea, vomiting, abdominal pain and Kussmaul respirations were observed as well.

The 154 cases in which these criteria were fulfilled were divided into five groups, according to the classification described by Rabinowitch and associates,⁶ which takes into consideration such factors as age, duration of mental symptoms, degree of consciousness, the presence of coffee ground vomitus, the presence of infection, blood pressure, plasma carbon dioxide-combining power, the level of urea in the blood and the presence of such associated conditions as tuberculosis, heart disease, vascular sclerosis and pregnancy. The results of this analysis are given in the table.

3. Somogyi, M.: A Method for the Preparation of Blood Filtrates for the Determination of Blood Sugar, J. Biol. Chem. **86**:655-663, 1930. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, St. Louis, C. V. Mosby Company, 1938, pp. 173-174.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, pp. 296-298.

5. Peters and Van Slyke,⁴ pp. 639-641.

6. Rabinowitch, I. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma: Investigation of Mortalities and Report on Severity Index for Comparative Studies, Ann. Int. Med. **12**:1403-1428, 1939.

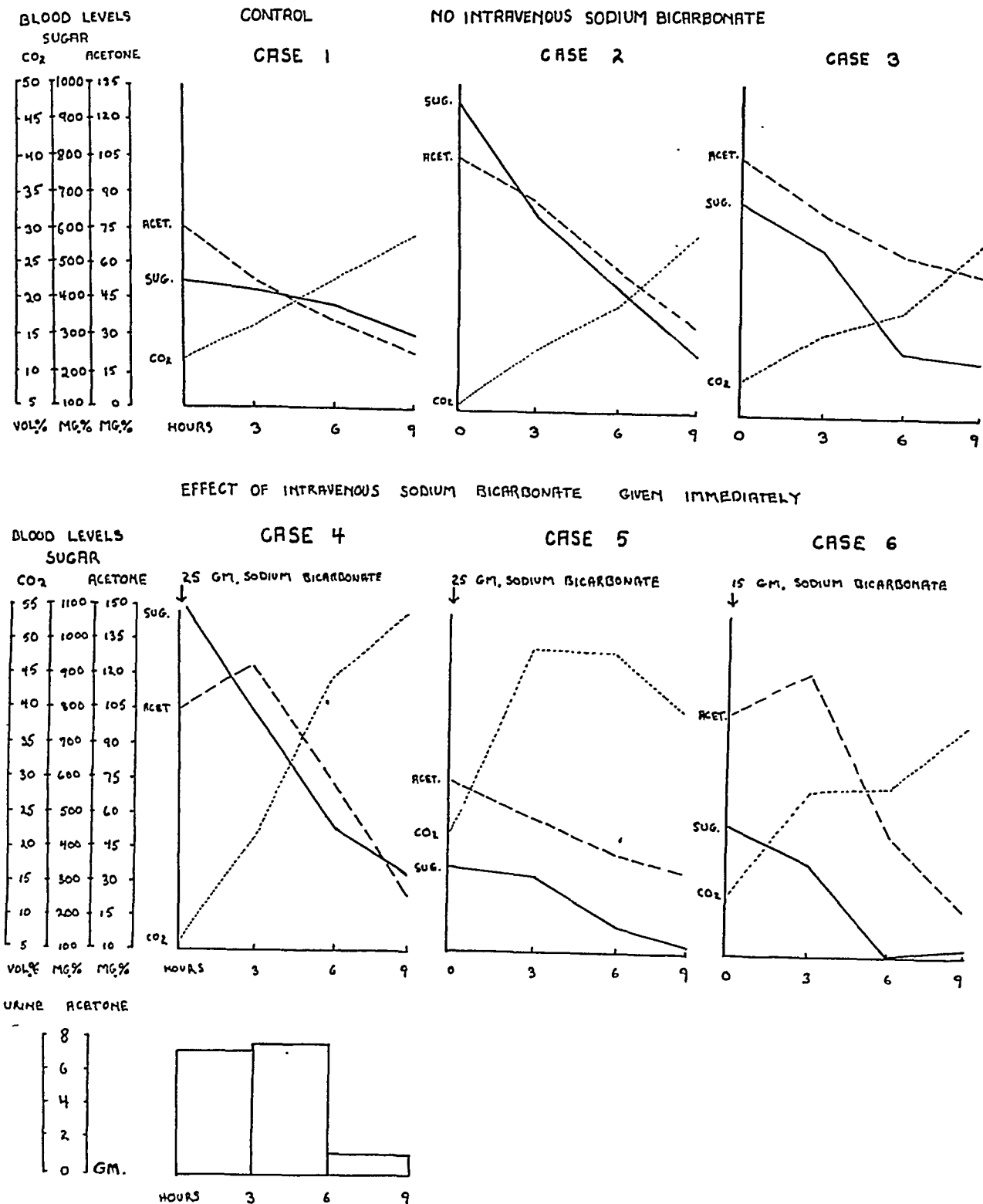


Fig. 1.—The effect of the intravenous administration of sodium bicarbonate on blood sugar, carbon dioxide-combining power and the level of acetone in the blood and urine. Cases 1 to 3, sodium bicarbonate not administered. Cases 4 to 6, sodium bicarbonate administered intravenously at the beginning of the nine hour period of observation.

EFFECT OF INTRAVENOUS SODIUM BICARBONATE GIVEN ON THE THIRD HOUR

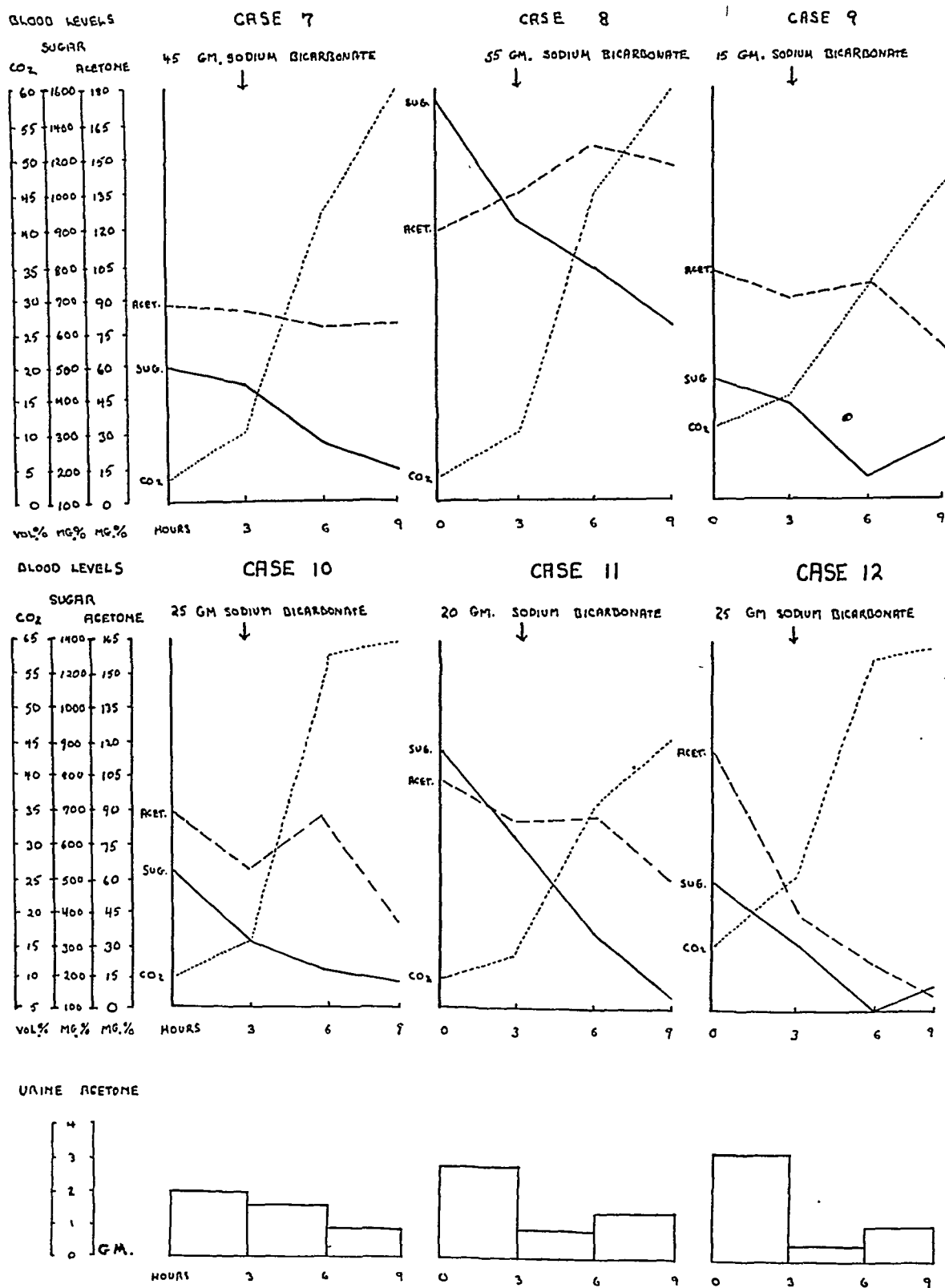


Fig. 2 (cases 7 to 12).—The effect of the intravenous administration of sodium bicarbonate at the third hour of a nine hour period of observation of the changes in blood sugar, carbon dioxide-combining power and the level of acetone in the blood and urine.

RESULTS AND COMMENT

In the 3 control cases, in which no intravenous treatment with sodium bicarbonate was given, the carbon dioxide-combining power rose progressively during the nine hours of study after admission to the hospital. In 2 cases the rise was 15 volumes per cent, and in 1 case it was 23 volumes per cent (fig. 1, cases 1, 2 and 3). In the control cases the ketones in the blood fell progressively in inverse proportion to the rise of carbon dioxide-combining power.

The average rise of carbon dioxide-combining power in the 9 cases in which sodium bicarbonate was given intravenously, in doses varying from 15 to 55 Gm., was over twice as great as in the controls, but the results were not consistent. Whereas in 4 cases the maximal rise was 60 to 65 volumes per cent, in 2 cases the rise was no greater than that in the controls. Elevation of the carbon dioxide-combining power produced no effect on the mental state, the blood pressure, the output of urine or any other vital sign, but Kussmaul respirations were relieved with great consistency. This last-named effect is interesting, since the physiology of air hunger in diabetic ketosis has never been adequately explained. Although hyperventilation has been observed after the administration of ketone bodies containing the enol complex,⁷ most workers agree that a lowered p_H and carbon dioxide-combining power of the serum act directly on the respiratory center. We feel that the latter explanation is more correct. Kussmaul respirations were relieved immediately after administration of sodium bicarbonate, after the p_H and carbon dioxide-combining power had been corrected but before any appreciable drop in the level of ketones in the blood was observed.

The effect of intravenous administration of sodium bicarbonate on the level of ketones in the blood was unexpected. In two thirds of the cases the ketones increased during the three hours following intravenous administration of sodium bicarbonate. The greatest rise (23 mg. per hundred cubic centimeters) occurred in a case of extremely severe ketosis in which a large amount of sodium bicarbonate was given (fig. 2, case 8). In 2 cases the increase was small but definite enough to be significant (fig. 2, cases 9 and 11). In one third of the cases the level of ketones in the blood failed to rise; the rate of fall was slower than that in the control cases.

The total output of ketones in the urine was measured in 4 cases in which sodium bicarbonate was given intravenously. In 3 cases the excretion of ketones in the urine was less immediately after the administration of sodium bicarbonate than during the subsequent three hours (fig. 1, case 4, and fig. 2, cases 11 and 12). This decrease is doubly significant, because in 2 of the 3 cases an increase in the ketones in the blood

7. Wright, S.: *Applied Physiology*, New York, Oxford University Press, 1937, p. 572.

occurred concomitantly with a lessened amount in the urine. Although in the fourth case the ketones in the blood increased after sodium bicarbonate was given, the amount in the urine fell progressively (fig. 2, case 10).

This rise in blood ketones and fall in urinary ketones immediately following the intravenous administration of bicarbonate is interesting. Sodium bicarbonate might accelerate the breakdown of fatty acids or liberate ketones from the tissues, but if this were true, one would expect an increased rather than a decreased amount of ketones in the urine. This divergence of the levels of ketones in the blood and the urine following administration of an alkali must indicate that the changes are due to a transitory decrease in elimination rather than to increased production of ketones. In any case, it seems safe to say that intravenous administration of sodium bicarbonate has no antiketogenic action in cases of diabetic ketosis and that it does not facilitate the elimination of ketones that have already accumulated in the blood and urine.

Study of the mortality rates for 154 cases of severe diabetic ketosis has likewise failed to show any benefit from sodium bicarbonate therapy.

One difficulty in evaluating any single therapeutic factor in diabetic ketosis by the case study method has been the great variation in the severity of disease in individual cases. Mortality statistics are of little comparative value when one clinic studies a group of unconscious patients who have infection or arteriosclerosis and another studies semiconscious patients in whom ketosis is not complicated by any other serious factor. When a clinical yardstick, such as Rabinowitch's classification, is used to estimate the severity of disease, much more significant comparisons can be made.

In 47 of the 154 cases of diabetes with associated ketosis in which adequate data were available, 10 Gm. or more of sodium bicarbonate was given intravenously within the first twenty-four hours of treatment. So few deaths occurred in the cases of mild ketosis that the figures are of little comparative value. The mortality for cases of moderately severe ketosis in which sodium bicarbonate therapy was given was slightly higher than that for those in which this treatment was not employed (40 per cent, as compared with 33 per cent). The mortality for control cases of severe ketosis was about the same as that for cases in which treatment was given (table). In general, the mortality was strikingly similar for the two groups of cases.

SUMMARY

Twelve cases of diabetic ketosis were studied to determine the effect of intravenous administration of sodium bicarbonate on the level of blood sugar, carbon dioxide-combining power and the level of ketones in the blood and urine early in the period of treatment.

Intravenous injection of sodium bicarbonate raised the carbon dioxide-combining power and relieved Kussmaul respirations but was without effect on the level of sugar in the blood. No antiketogenic action was observed, but rather a slight tendency in some patients for the elimination of ketones to be delayed.

One hundred and fifty-four cases of diabetic ketosis, in approximately one third of which sodium bicarbonate was administered, were classified into five groups according to the intensity of the ketosis. The mortality rates both for the cases in which treatment was given and for control cases were determined.

If the severity of diabetic ketosis is taken into proper consideration in each case, there seems to be no difference in mortality between those cases in which treatment was with sodium bicarbonate and those in which no alkali was given.

There seems to be no practical basis for sodium bicarbonate therapy in the treatment of diabetic ketosis.

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RHEUMATIC PNEUMONIA

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The occurrence of various pulmonary symptoms and signs in the course of acute and recurrent rheumatic fever has always perplexed clinicians. It is only natural that many writers should attribute them to a specific rheumatic infection. This specificity for the pulmonary changes has been accepted by some clinicians as a corollary to the pathologic alterations in other parts of the body occurring in rheumatic fever.

To Stoll,¹ is given the credit for first speaking of "rheumatic pleurisy" and "rheumatic peripneumonia," in 1788. Years later, in 1813, Chomel² mentioned pulmonary rheumatism. The real impetus to the problem was given by Latham,³ in 1845, and Fuller,⁴ in 1854. Latham, in a prophetic vein, wrote: "Such forms of pulmonary inflammation are portentous ingredients in the clinical history of acute rheumatism, and give a fearful interest to it," and Fuller went even further by claiming that "the pulmonary inflammation is due to the same cause of irritation, the same morbid agent which excites the articular and cardiac affections." For over eighty-five years the clinical and pathologic statistics of Latham and Fuller have been repeatedly cited, and over this same period names of many pathologists and clinicians have been added to the roster of supporters of the theory of the specificity of the pulmonary lesions occurring in acute rheumatic fever.

Ormerod,⁵ in 1858, maintained that pneumonia constituted a regular part of "these two diseases, rheumatism and continued fever." -In a

From the laboratories and wards of the Mount Sinai Hospital.

1. Stoll, M.: *Rationis medeni*, Vienna, 1788.

2. Chomel, A. F.: *Essai sur le rhumatisme*, Thesis, Paris, no. 63, 1813.

3. Latham, P. M.: *Lectures on Subjects Connected with Clinical Medicine, Comprising Diseases of the Heart*, London, Longmann [and others], 1845, vol. 1, pp. 159-179.

4. Fuller, H. W.: *On Rheumatism, Rheumatic Gout, and Sciatica*, New York, S. S. & W. Wood, 1854, pp. 249-256.

5. Ormerod, E. L.: *Observations on Certain Forms of Disease of the Lungs*, Brit. M. J., 1858, pp. 1025-1028.

similar vein wrote Howard ⁶ in 1885, Cheadle ⁷ in 1888 and Garrod ⁸ in 1890. Garrod said:

In a considerable number of cases of rheumatic fever, inflammatory lesions of the lungs or pleura are observed; far less commonly, it is true, than endocarditis or pericarditis, but still with sufficient frequency to justify their inclusion among the more important accidents of the rheumatic state.

He expressed the opinion that the inflammatory lesion was a specific rheumatic pneumonia.

In the present century the question of the specificity of rheumatic pleurisy seems to have been answered in the affirmative by the work of Mosler,⁹ of Rolly¹⁰ (who found pleuritis in 2.4 per cent of 3,620 cases and who wrote that "diseases of the serous membranes are to be considered not as complications but rather as characteristics of the rheumatic disease, caused by the same cause as the acute articular rheumatism"), of Swift¹¹ (who found pleurisy in about 10 per cent of his patients with acute rheumatic fever) and of Paul¹² (who said: "It is questionable whether pleurisy should be regarded as a complication rather than another manifestation of rheumatic disease of the serous membranes of which pericarditis, pleurisy and even peritonitis are examples.").

The unanimity of opinion which existed in the past century in regard to rheumatic pneumonia and exists today in regard to rheumatic pleurisy is absent when the problem of the pneumonic complications in acute rheumatic fever is brought forward. There is agreement that varied pulmonary symptoms and signs are constantly encountered during the course of rheumatic fever, and the clinical descriptions have been ably presented by Coombs,¹³ Rabinowitz,¹⁴ Findlay,¹⁵ Coburn¹⁶ and others.

6. Howard, R. P.: Rheumatism, in Pepper, W.: A System of Practical Medicine by American Authors, Philadelphia, Lea Bros. & Co., 1885, vol. 2, pp. 19-69.

7. Cheadle, W. B.: Clinical Lecture on an Outbreak of Rheumatic Pneumonia, *Lancet* **1**:861-863, 1888.

8. Garrod, A. E.: A Treatise on Rheumatism and Rheumatoid Arthritis, Philadelphia, P. Blakiston, Son & Co., 1890, chap. 11, pp. 105-111.

9. Mosler, E.: Ueber rheumatische Entzündung der serösen Häute (sogenannte Polyserositis rheumatica), *Berl. klin. Wchnschr.* **47**:277-279, 1910.

10. Rolly, F.: Der akute Gelenkrheumatismus, Berlin, Julius Springer, 1920.

11. Swift, H. F.: Rheumatic Fever, (a) in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1930, vol. 1, p. 401; (b) in Cecil, R. L.: Text-book of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937.

12. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine* **7**:383-410, 1928.

13. Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood and Company, 1924.

14. Rabinowitz, M. A.: Rheumatic Pneumonia, *J. A. M. A.* **87**:142-144 (July) 17) 1926.

The onset is insidious during the course of active rheumatic fever, usually without evidences of congestive heart failure. The customary signs and symptoms of ordinary pneumonias, such as symptoms referable to the upper respiratory tract, chill, chest pain and rusty sputum, are absent. The physical signs are usually observed at the bases of one or both lungs, although they are frequently present in the upper lobes. There may be the characteristic signs of consolidation or only scattered rales and diminished breathing. The signs of resolution frequently seen in pneumonia are generally absent. The rapid disappearance of symptoms within a few days and the migratory and fleeting character of the consolidation, with rapid involvement of other sites, distinguish the clinical picture from that of lobar pneumonia or bronchopneumonia, usually encountered. The roentgenograms are interpreted as characteristic of one of the following conditions: intense congestion, edema, pneumonitis or infiltration, infarct or pneumonia.

The recent intensive pathologic restudy of the pulmonary changes occurring in rheumatic fever can be considered to have started with the report of Paul, who found in 30 cases that "in more than half there were evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or groups of lobules, which might be interpreted as an early or hemorrhagic stage of a broncho- or lobular pneumonia." He expressed the belief that sufficient evidence had not been accumulated to prove this lesion to be a specific manifestation of rheumatic fever, although it seemed to be a fairly characteristic finding.

At about the same time Naish¹⁷ described what he called a new type of pathologic consolidation of the lung in rheumatic fever and termed the condition "rheumatic lung." He was impressed by the characteristic macroscopic appearance of the affected parts, which was unlike that seen in any other form of pneumonia. The consistency was not unlike that of solid india rubber, very tough and nonfriable. The color was a shade of purplish red, homogeneous in tint on section. The most striking microscopic feature was an enormous endothelial proliferation, the cells apparently originating from the walls of the alveolar capillaries. Naish expressed the belief that the reactive process was identical with that described by Coombs as pathognomonic of rheumatic infection elsewhere in the body.

Even more emphatic about the specificity of rheumatic pneumonia was Fraser's¹⁸ report. In 2 cases of acute rheumatic fever he found the

15. Findlay, L.: Pulmonary Lesions in Rheumatism, *Arch. Dis. Childhood* 5:259-264, 1930.

16. Coburn, A. F.: *The Factor of Infection in the Rheumatic State*, Baltimore, Williams & Wilkins Company, 1931.

17. Naish, A. E.: The Rheumatic Lung, *Lancet* 2:10-14, 1928.

18. Fraser, A. D.: The Aschoff Nodule in Rheumatic Pneumonia, *Lancet* 1:70-72, 1930.

pulmonary lesion in its acute stage characterized by vascular changes and proliferation and later by necrosis of alveolar cells and destruction of bronchi. It resembled an acute interstitial pneumonia. Fraser found what he considered to be typical Aschoff nodules in the interstitial tissue of the lung, most prominent in the interlobular septums.

Coburn¹⁹ found the changes in the lungs in rheumatic fever to consist of: subpleural and alveolar hemorrhage, with engorgement of the blood vessels; interstitial and alveolar edema; infiltration by wandering cells, with resultant massive accumulation of large mononuclear cells in clusters; round cells and, rarely, polymorphonuclear cells; deposition of a hyaline membrane along the walls of the alveolar sacs, and the absence of detectable micro-organisms in the affected areas. These lesions, like those in the skin, brain, kidneys and abdominal viscera, suggested alteration in vascular permeability with diapedesis and damage to the mesodermal tissues, accompanied in certain instances by inflammatory reaction. Coburn observed 45 instances of hemorrhagic pulmonary solidification among the 320 cases studied. He did not observe specific histologic structures (Aschoff bodies). In his book, Coburn¹⁶ stated, "The histological lesions regarded as specific in rheumatic disease have not been defined in the lung. This is believed due to the character of the tissue developing the rheumatic process."

Similarly, Klinge,²⁰ who had a most extensive experience with rheumatic fever, did not consider the pulmonary lesions as characteristic or specific. He noted, as did Paul, and also Coburn, inflammatory lesions with hemorrhagic foci and found difficulty in differentiating the roles played by chronic stasis and rheumatic inflammation in their pathogenesis. He never saw Aschoff bodies in the lung, although he observed the Aschoff nodules described by Fraser in the adventitia of the pulmonary artery. Similar nonspecificity was observed by Cook²¹ and Melnick.²²

Gouley and Eiman,²³ like Naish and Fraser, have emphasized in repeated communications the specificity of the lesions found in the lungs in rheumatic fever. They noted that the inflammatory pulmonary reaction

19. Coburn, A. F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, *Am. J. Dis. Child.* **45**:933-972 (May) 1933.

20. Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus, *Virchows Arch. f. path. Anat.* **286**:344-388, 1932.

21. Cook, G. T.: On the Association of Pulmonary Changes with Rheumatic Pericarditis, *Brit. J. Child. Dis.* **29**:264-276, 1932.

22. Melnick, P. J.: Pulmonary Changes in Rheumatic Fever, *Illinois M. J.* **73**:336-339, 1938.

23. Gouley, B. A., and Eiman, J.: The Pathology of Rheumatic Pneumonia, *Am. J. M. Sc.* **183**:359-381, 1932.

consisted of an interstitial perivascular exudate of large endothelial cells, identical morphologically with those found in lesions in the heart caused by rheumatic fever and considered pathognomonic of that disease. They concluded by saying, "We therefore consider that in many virulent cases a characteristic rheumatic pneumonia is to be found." Likewise, Lutembacher²⁴ claimed the existence of a rheumatic pneumonia, which was characterized grossly by homogeneous areas of hepatization and microscopically by leukocytic alveolitis without fibrinous exudate and by a marked hemorrhagic edema and exudative lesion in the alveoli.

The most provocative contributions to the already long list have been added recently by Masson, Riopelle and Martin²⁵ and Hadfield.²⁶ The former studied 13 cases of rapidly fatal, active rheumatic fever, all but 1 of which were in infants, with Aschoff bodies present in the heart in all cases. The outstanding changes were: (a) alveolitis, which was edematous, catarrhal, serofibrinous or fibrinohemorrhagic in character, with a seroalbuminous alveolar exudate, poor in fibrin and blood elements, but filled with alveolar cells; (b) hyaline membranes in the terminal bronchioles in 10 of the 13 cases, and (c) a proliferative, fibroblastic interstitial lesion. No Aschoff bodies were found in the lungs. Masson, Riopelle and Martin concluded:

To our knowledge, the pneumopathy which we have just described is particular to young persons with rheumatic fever. Without a doubt, Aschoff bodies, the "signature" of rheumatic fever, do not occur in this condition, and the primary lesions which constitute the pneumopathy are not strictly exclusive. But their extreme frequency in the course of infantile rheumatism, their combination, their extension and their anatomic features contribute to the individuality of the pathologic picture.

Hadfield recently reported 5 cases of the acute stage of rheumatic fever in young people and recorded changes similar to those described by Masson. Hadfield described the primary lesion as widespread fibrinous alveolitis, followed by an infiltration of mononuclear cells, which developed slowly but eventually became copious and diffuse. In cases with a fatal outcome this primary lesion was complicated by formation of a hyaline pseudomembrane in most of the alveolar ducts in the consolidated lung. This process occurred in the finest ramifications of the airways in the presence of a viscid albuminous exudate and a period of severe inspiratory dyspnea.

24. Lutembacher, R.: Congestion suraigüe oedémateuse du poumon dans la maladie de Bouillaud, *Rev. du rhumatisme* **3**:257-274, 1936.

25. Masson, P.; Riopelle, J. L., and Martin, P.: Poumon rhumatismal, *Ann. d'anat. path.* **14**:359-382, 1937.

26. Hadfield, G.: The Rheumatic Lung, *Lancet* **2**:710-712, 1938.

We have studied the problem of the pulmonary changes in rheumatic fever from a different aspect, choosing our cases in consecutive order, eliminating none of them because of the absence of clinical or macroscopic evidences of pneumonia or consolidation. In this manner we believe the evolution of the entire pulmonary picture may be unfolded in chronologic sequence and the histologic changes correlated with the approximate duration of the disease as determined from the clinical history. Toward this end we have ascertained the duration of the illness at home before admission to the hospital, the time spent in the institution before death and the number of previous attacks of rheumatic fever, as well as the presence of chronic valvular changes from the preceding attacks. This has enabled us to study the pathologic changes in the lung in relation to the acuteness and the duration of the rheumatic fever.

Forty-five cases of acute rheumatic heart disease were studied at autopsy and were divided into three groups on the following basis: (1) absence of a previous history of rheumatic fever, no evidence of chronic valvular disease and an acute, rapidly fatal initial attack, (2) a previous history of rheumatic fever, evidence of chronic valvular disease and a rapidly fatal course in the last admission, and (3) chronic rheumatic cardiovalvular disease with the fatal attack lasting a considerable time.

GROUP 1

This group includes 14 cases in which the patient died during the first attack of acute rheumatic fever. The ages of the patients varied from 19 months to 25 years; 7 were below 5 years of age, 2 were between 5 and 10, 3 were between 10 and 20, 1 was 22 and 1 was 25. The entire stay in the hospital, from admission to death ranged from a few hours to six weeks. Two patients died a few hours after admission; 3 died in one day, 2 in two days, 2 in five days and 1 each in six, seven, ten, twenty and forty-two days.

The earliest lesion in the lungs in acute rheumatic fever was observed in the case of a boy 7 years old who had had no previous attack, who had been ill only a short time and who died as he entered the hospital admitting room, before he could be sent to the ward. No chronic valvular disease was observed at autopsy, but acute verrucous endocarditis of all valves, acute fibrinous pericarditis and rheumatic myocarditis, with many Aschoff bodies, were found. The striking histologic alterations in the lungs were the marked edema and severe congestion with areas of hemorrhage. The alveoli were filled with desquamated epithelial cells with large nuclei and clear pale cytoplasm. The edema fluid did not show any fibrin. A striking feature was the presence of hyaline eosinophilic bands along the respiratory bronchioles and alveolar ducts. This

hyaline material did not stain for fibrin, contained fat, was not doubly refractile and stained yellowish orange with sudan, deep red with Mallory's aniline blue acid fuchsin and vermillion—purplish red with phosphotungstic acid hematoxylin. The arteries, arterioles, veins and bronchi were normal. A similar opportunity to study an early pulmonary lesion occurred in the case of an infant of 19 months who died after one day in the hospital. The lungs were firm and fleshy, and only a few aerated patches could be detected. There were marked congestion, edema and desquamation of epithelial cells into the alveoli, which were literally bulging with edema fluid, desquamated cells and erythrocytes. The

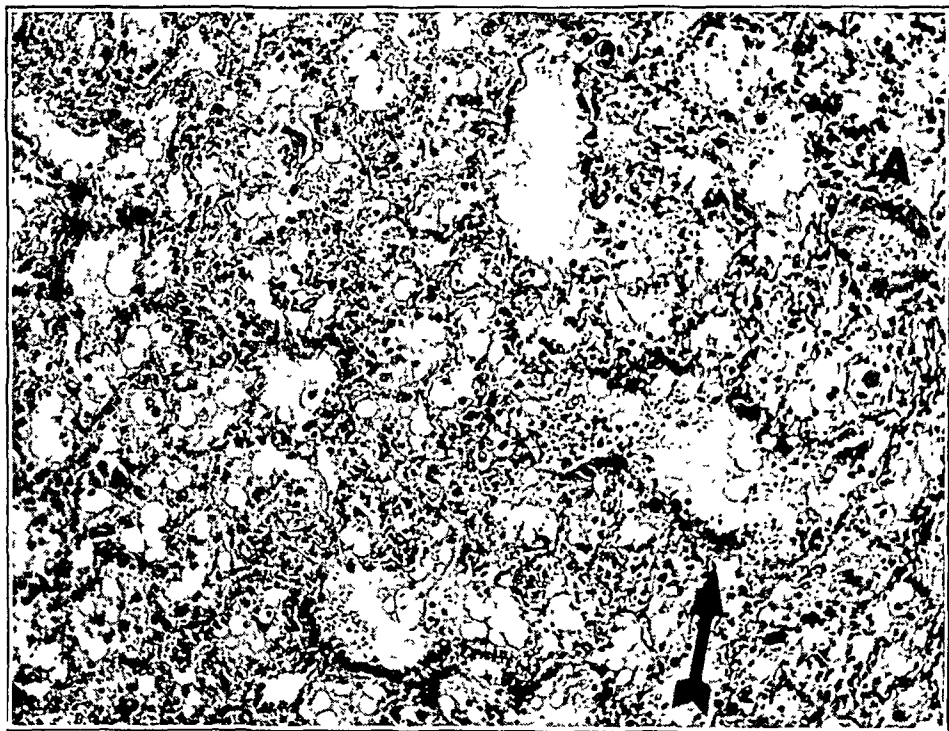


Fig. 1.—A section of the lung of a 4 year old child who died during the first attack of rheumatic fever after only two days in the hospital. The alveoli are filled with edema fluid, erythrocytes and numerous mononuclear cells. Note the striking hyaline bands (*A*) along the walls of the respiratory bronchioles.

edema fluid extended into the septal walls and interlobular septums. The respiratory bronchioles were filled with hyaline eosinophilic bands.

From 2 cases in which the patients died within a week after the onset of the attack of rheumatic fever, we deduced further steps in the sequence of events. In addition to the features just mentioned the alveolar septums had become moderately thickened and edematous and in many areas contained large mononuclear cells in their stroma. The large mononuclear epithelial cells desquamated into the alveoli already

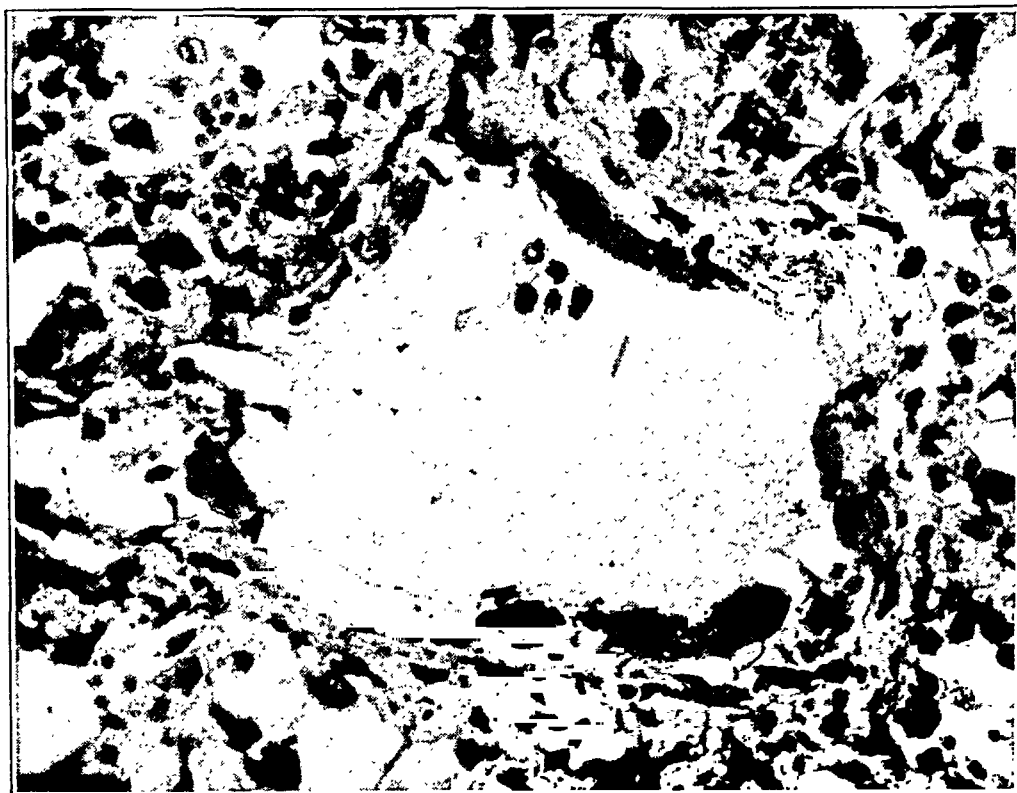


Fig. 2.—High power magnification of the hyaline bands marked *A* in figure 1.

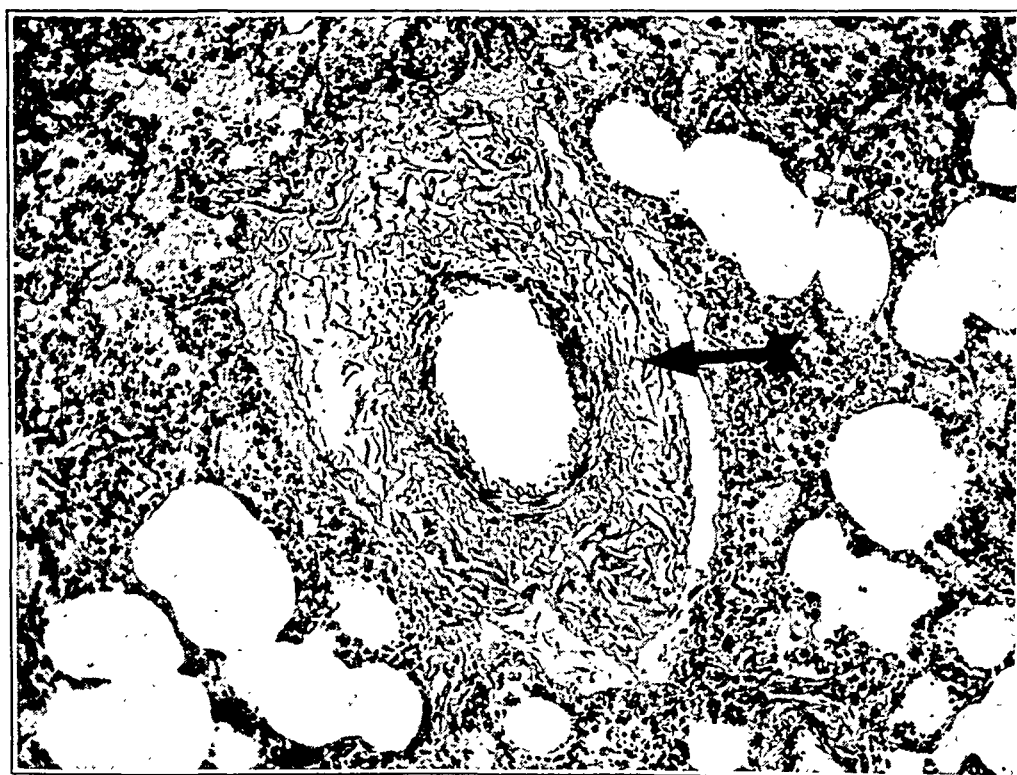


Fig. 3.—Periarterial edema in the lung of the child referred to in figure 1.

showed phagocytosis of erythrocytes and, in some areas portions of the hyaline membranes. Hyaline thrombi occurred frequently in the alveolar capillaries. In cases in which autopsy was done after the second or third week of illness, the subpleural areas were observed to contain an infiltration of mononuclear cells. In some sections there were definite areas of fibrosis and various stages of organization. The arteries had already become thickened with increased periadventitial tissue, which in some instances had undergone fibrinoid degeneration. Occasionally small arteries were seen to be occluded by thrombi.

From the study of the foregoing 14 cases in which the patients died in the initial attack of rheumatic fever and in which there were no complications of stasis due to previous cardiovalvular disease, one may reconstruct the chronologic change in the lungs as follows: (1) considerable edema, first intra-alveolar, then septal and interlobular; (2) congestion of alveolar capillaries and diapedesis of erythrocytes in large numbers into the alveoli; (3) desquamation into the alveoli of large mononuclear cells, which later showed phagocytosis; (4) formation of hyaline membranes in the respiratory bronchioles and alveolar ducts in 50 per cent of the cases; (5) beginning thickening and infiltration of the interlobular septums with mononuclear cells, beginning fibrosis and organization, and (6) thickening of smaller arteries and occasional occurrence of hyaline thrombi in them. Grossly the lungs showed patchy foci of dark red, fleshy, noncrepitant, nonaerated areas.

This study of the chronologic development of pulmonary changes was continued in the remaining 31 cases of acute rheumatic fever, in which one or more previous attacks had resulted in chronic cardiovalvular disease of the mitral, aortic or tricuspid valve. These cases were divided according to the duration of the fatal attack of rheumatic fever before autopsy, with death occurring three weeks, six weeks or longer than six weeks after the onset of the illness.

GROUP 2

Subgroup A.—In 10 cases of previous rheumatic cardiovalvular disease death occurred within three weeks after the onset of the fatal attack. The ages of the patients ranged from 7 to 38 years. It is difficult to state definitely how many previous attacks had occurred in each case; in 4, however, a history of only one previous attack was obtained. Disease of the mitral valve was present in all cases; in addition the aortic valve was involved in 7 cases and the tricuspid in 3. Aschoff bodies occurred in 8 cases and acute fibrinous pericarditis in 3 cases.

In 3 of these 10 cases the histologic picture encountered in the preceding group was observed, namely, alveoli everywhere filled with edema fluid, erythrocytes and medium and large desquamated epithelial

cells; extreme congestion of the alveolar capillaries, and hyaline membranes outlining the respiratory ducts. In addition, in these 3 cases, the epithelial cells had already undergone fragmentation and exhibited phagocytosis of erythrocytes and pigment.

In the other 7 cases the evolution of the pathologic process in the lung tended to run thus: Beneath the thickened pleura were areas of fibrosis and pseudogland formation suggesting regeneration of alveolar epithelium, large areas of atelectasis with thickened alveolar septums and congestion, chronic edema and numerous clumps of pigment-laden macrophages and epithelial cells showing erythrophagocytosis. There were scattered emphysematous alveoli, intimal hyperplasia and medial thickening of the medium-sized and larger pulmonary arteries, areas of organization and carnification, thickening of the interalveolar septums, and thrombi in some of the smaller arteries.

In 5 of the 10 cases pneumonia was present at death. In 1 case the exudate was predominantly hemorrhagic; in the others the usual picture of confluent bronchopneumonia was present, with polymorphonuclear leukocytes, erythrocytes, fibrin, etc.

Subgroup B.—In 11 cases one or more previous attacks of rheumatic fever, with subsequent chronic cardiovalvular disease, occurred and the final fatal attack lasted up to six weeks from the onset of symptoms to death. The ages ranged from 3 to 45 years. A defect of the mitral valve occurred in every case, together with a defect of the aortic valve in 6 cases, of the tricuspid valve in 5 cases and of the pulmonary valve in 1 case; fibrinous pericarditis was present in 6 cases, and Aschoff bodies were seen in 7 cases. In these 11 cases we were impressed by the chronic character of the pulmonary changes. The pleura was thickened and vascularized, and the subpleural area showed an increase in lymphocytes. The alveoli were more frequently collapsed than in the preceding group, and their walls were thickened and in places completely obliterated. The walls of the alveolar septums were markedly thickened. We observed increased numbers of heart failure cells, desquamated epithelial cells containing erythrocytes; thickened and congested alveolar capillaries; thickened arteries with perivascular fibrinoid degeneration and vacuolation of the media; thrombi with infarctions, areas of atelectasis and collapse, and scattered areas of pneumonia. Bronchopneumonia occurred in 5 cases, and the infiltration was characteristically peribronchial, with polymorphonuclear leukocytes, fibrin and bacteria, and with polymorphonuclear exudate in the bronchi and occasional destruction of the bronchial wall.

In 4 cases of this group, those of patients aged 3, 6, 13 and 14, with a history of fairly acute disease and the presence of Aschoff bodies and fibrinous pericarditis, there occurred a reaction similar in some respects to that seen in the first group, in which the initial attack of rheumatic

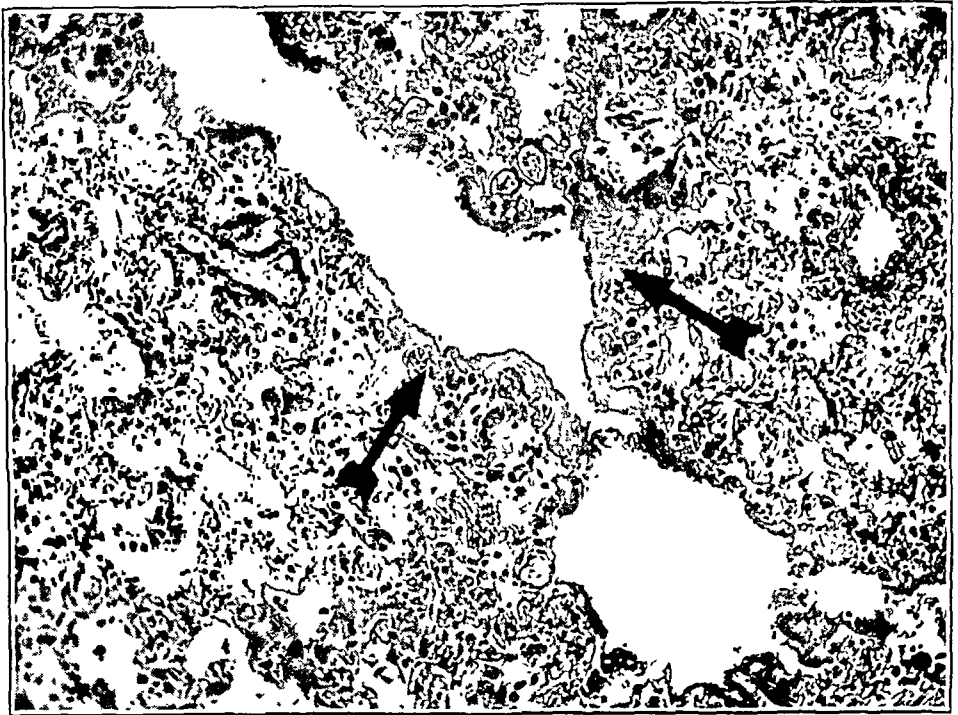


Fig. 4.—Hyaline membranes in the respiratory bronchioles in the lung of a 4 year old child who died during the first attack of rheumatic fever after ten days in the hospital.

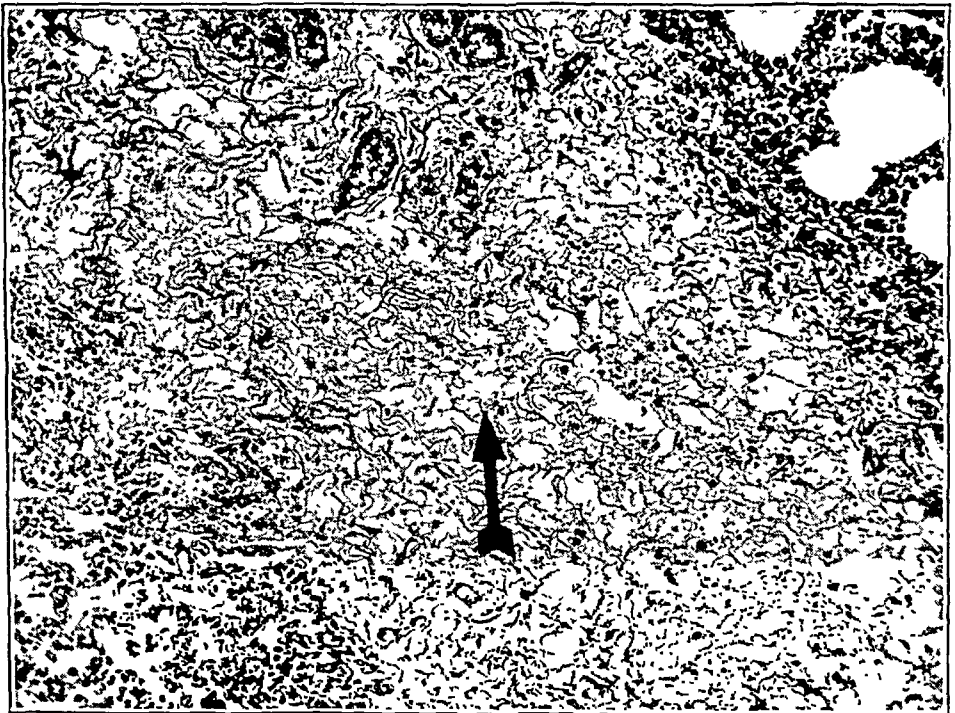


Fig. 5.—Striking widening of the interlobular septum of the lung due to edema in the case of the child referred to in figure 4.

fever was fatal. We observed marked congestion, diapedesis of erythrocytes into alveoli, transudation of edema fluid into alveoli and alveolar septums, congestion of alveolar capillaries, desquamation of epithelial cells into alveoli and hyaline membranes outlining the respiratory bronchioles and alveolar ducts. In only 1 of these 4 cases were there also the marked chronic stages seen in the others.

GROUP 3

The last group studied comprised 10 cases in which there had been at least one previous attack of rheumatic fever and in which the

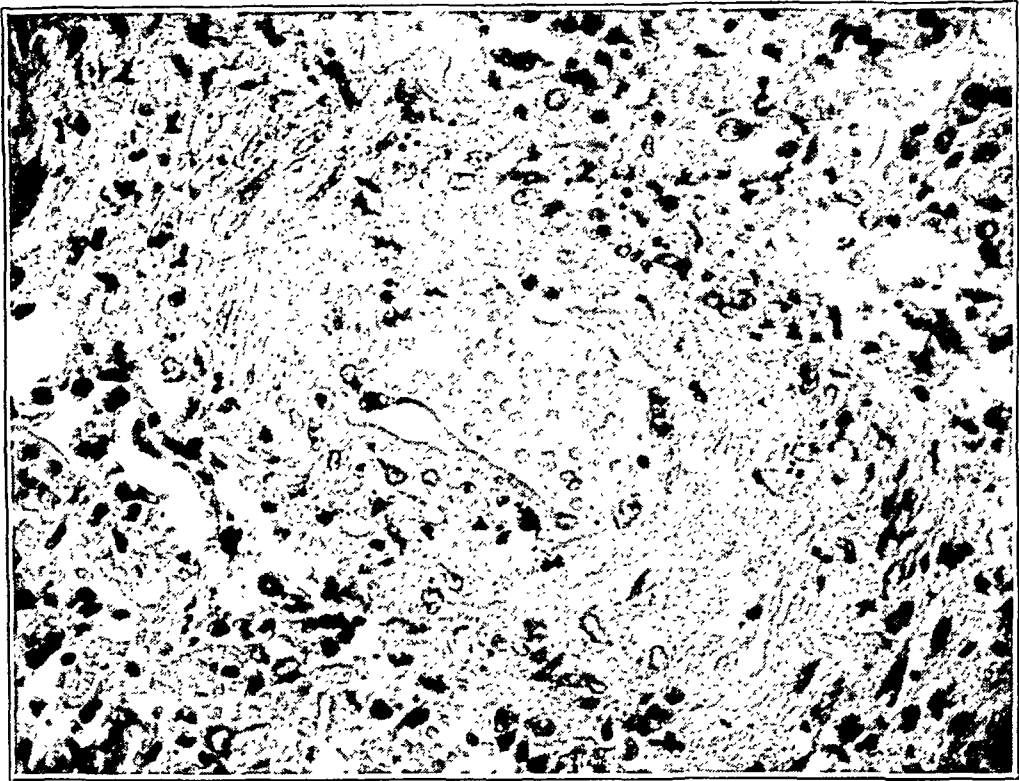


Fig. 6.—A section of the pulmonary artery of a 17 year old patient with chronic rheumatic cardiovalvular disease who died during an attack of acute rheumatic fever two months after admission to the hospital. The wall of the artery shows marked necrosis, and an adventitial and periarterial inflammatory reaction is evident.

total duration of the final fatal attack had been longer than six weeks. The chronic cardiovalvular lesion affected the mitral valve in 9 cases; in 5 of these the aortic valve, in 4 the tricuspid valve, was also involved. In 1 case the aortic valve alone was affected. Fibrinous pericarditis was present in 4 instances and Aschoff bodies in 6 instances. The ages of the patients ranged from 12 to 51 years.

Here we encountered the picture mainly of organization and fibrosis. In only a few instances did we see the acute phase of congestion, edema

and desquamation of epithelial cells into the alveoli. The common lesion consisted of atelectasis and collapse, with areas of interstitial fibrosis; formation of new blood vessels; marked thickening of the alveolar septums; organization of the alveolar exudate; destruction of alveolar structure by wide bands of connective tissue; large numbers of heart failure cells; peribronchial thickening; hypertrophy of the musculature of the respiratory bronchioles; occlusion of the pulmonary arteries by thrombi; marked intimal proliferation and narrowing of the arteries and arterioles, going on to complete obliteration, and perivascular infiltration and thickening of the media. In 2 cases hyaline membranes lined the respiratory bronchioles and the alveolar ducts. In 5 cases there occurred patchy bronchopneumonia of various lobes, which was no different than the usual bacterial pneumonias seen as complications of any other chronic disease.

CONTROL GROUPS

In order to eliminate the possibility that the lesions which we have described in the lungs in cases of acute rheumatic fever might have occurred as a result of congestive heart failure, we studied the following groups of controls: 20 cases of chronic rheumatic cardiovalvular disease, mitral stenosis, in which the patient died of another disease or of chronic heart failure without any evidences of acute rheumatic fever; 23 cases of acute and chronic disease of the coronary arteries in which death was due to heart failure, and 16 cases of hypertension, either essential or malignant or due to chronic glomerulonephritis, with cardiac failure.

In none of the 20 cases of mitral stenosis in which death was due to another, unrelated disease or to chronic cardiac failure without acute rheumatic fever did we observe the hyaline membranes that we have seen to be conspicuous in many cases of acute rheumatic fever. We did find the chronic condition in the lungs described in the cases in which previous rheumatic attacks had occurred and in which death had terminated an acute phase of rheumatic fever lasting for several weeks. The lungs in these 20 control cases presented chronic congestion and edema, numerous heart failure cells, intra-alveolar fibrosis, fibroblastic proliferation, organization of alveolar exudate, thickening of the pleura with vascularization, atelectasis with carnification, thickened alveolar septums, thickening of arteries and arterioles, multiple infarcts, septal thickenings, emphysema and patchy areas of ordinary terminal bacterial bronchopneumonia.

There was no evidence of hyaline membranes in the lungs in the 23 control cases of acute and chronic coronary arterial disease in which death was due to cardiac failure, and the only changes in the lungs were chronic ones characteristic of long-standing pulmonary congestion.

In the 16 control cases of hypertensive heart disease with failure the picture was similar to that just described. In 1 case, that of a patient aged 23 who died in uremia of chronic glomerulonephritis with hypertensive cardiac disease and mild failure, we found hyaline membranes lining the respiratory ducts, similar in appearance to those occurring in the cases of acute rheumatic fever.

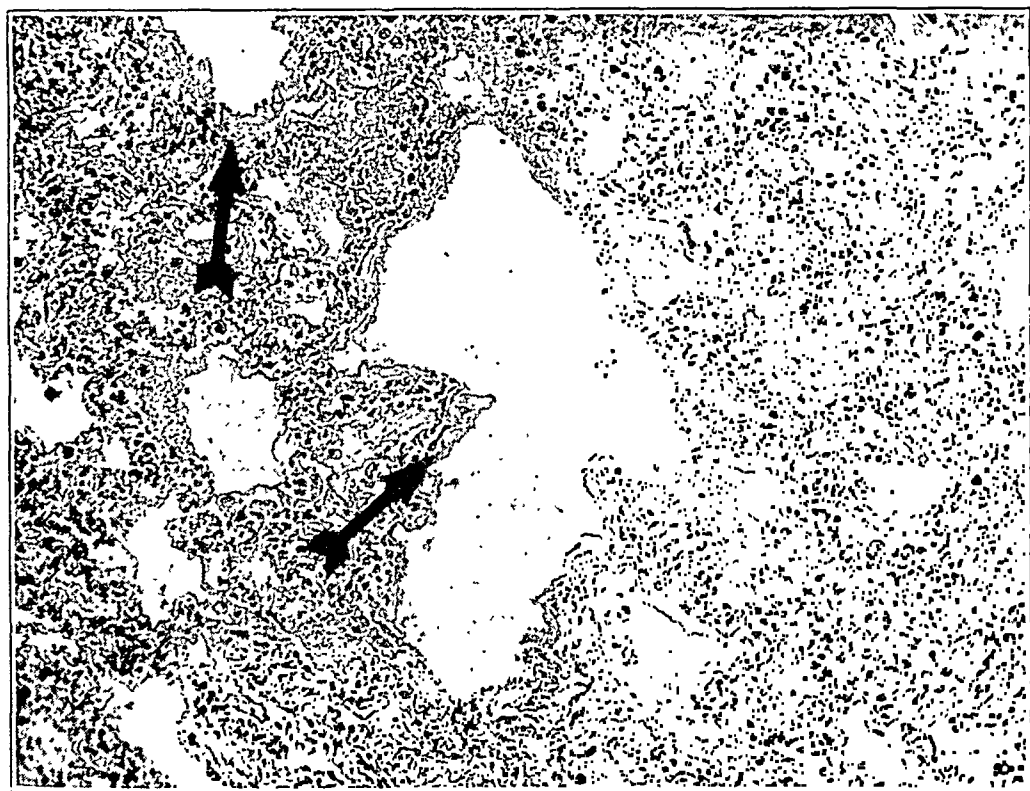


Fig. 7.—Hyaline bands along the walls of the respiratory bronchioles of a 23 year old patient with chronic glomerulonephritis who died in uremia. These bands are similar to those occurring in the lungs in cases of acute rheumatic fever.

HYALINE MEMBRANES IN THE LUNGS

Before entering on a discussion of the occurrence and pathogenesis of hyaline membranes in the lungs it is necessary to study briefly the anatomy of the bronchial tree. In their book on epidemic respiratory disease, Opie, Blake, Small and Rivers²⁷ have given this description:

It is convenient to designate as respiratory bronchioles the terminal ramifications of the bronchi; they are lined by a single layer of columnar ciliated cells passing over into cuboidal non-ciliated epithelium and are beset with small air sacs lined

27. Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease, St. Louis, C. V. Mosby Company, 1921.

by flat cells or epithelial plates similar to those of the alveoli elsewhere. The respiratory bronchiole by branching along its course or at its end is continued into several alveolar ducts which unlike the respiratory bronchioles have no cubical or columnar epithelium but are closely beset by alveoli lined by flat epithelial plates. The alveolar duct is recognized by the absence of cuboidal epithelium and the presence of bundles of smooth muscle which occur in the wall. The infundibula or alveolar sacs arise as branches from the alveolar ducts and like them are beset with alveoli but smooth muscle does not occur in their walls. The base of the infundibulum is wider than its orifice.

The formation of a layer of hyaline material on the inner surface of alveolar ducts and infundibula in epidemic influenza has been described by LeCount²⁸; Goodpasture and Burnett²⁹; Wolbach³⁰; Klotz³¹; MacCallum³²; Opie, Blake, Small and Rivers²⁷; Wolbach and Frothingham³³; Brannan and Goodpasture,³⁴ and Opie.³⁵ Klotz stated that this material had none of the staining reactions of fibrin and suggested it was made up of necrotic cells of the septum, which previously had suffered edema and circulatory interference. For a long time the occurrence of hyaline membranes in the lungs was considered characteristic of influenza.

Wolbach and Frothingham demonstrated, however, that the hyaline membrane in the alveolar ducts was an effect produced by air forced into exudate. They did not know of what the hyaline membrane was composed but expressed the opinion that it was related to the action of the air and the virus on some of the body fluid or exudates in epidemic influenza and not to degenerated epithelium. They based their conclusions on 2 cases in which the air had escaped from the lungs into the mediastinum with the development of the same hyaline membrane in the tissues of the mediastinum, where no epithelium existed. In both cases pneumococcic pericarditis and an acute infiltration of the fat and

28. LeCount, E. R.: The Pathologic Anatomy of Influenzal Bronchopneumonia, *J. A. M. A.* **72**:650-652 (March 1) 1919; Disseminated Necrosis of Pulmonary Capillaries in Influenzal Pneumonia, *ibid.* **72**:1519-1520, (May 24) 1919.

29. Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, *U. S. Nav. M. Bull.* **13**:177-197, 1919.

30. Wolbach, S. B.: Comments on the Pathology and Bacteriology of Fatal Influenza, *Bull. Johns Hopkins Hosp.* **30**:104-109, 1919.

31. Klotz, O.: The Pathology of Epidemic Influenza, in Publications from the University of Pittsburgh School of Medicine, 1919, pp. 207-285.

32. MacCallum, W. G.: Pathology of the Pneumonia Following Influenza, *J. A. M. A.* **72**:720-723 (March 8) 1919.

33. Wolbach, S. B., and Frothingham, C.: The Influenza Epidemic at Camp Devens in 1918, *Arch. Int. Med.* **32**:571-600 (Oct.) 1923.

34. Brannan, D., and Goodpasture, E. W.: The Pathology of Pneumonia Caused by *Bacillus Influenzae* During an Interepidemic Period, *Arch. Int. Med.* **34**:739-756 (Dec.) 1924.

35. Opie, E. L.: The Pathologic Anatomy of Influenza, *Arch. Path.* **5**:285-304 (Feb.) 1928.

areolar tissue of the mediastinum were present. Air bubbles also penetrated the mediastinal tissues, and wherever the air came in contact with this exudate the hyaline membrane was found. They expressed the belief that the air must be under some tension in its contact with the exudate before the membrane could be formed.

Confirmation of this concept was then brought forward by Farber and Sweet,³⁶ who observed membranes lining the respiratory ducts and alveoli in fetuses in which death had been due to intrauterine asphyxia. The membranes had the appearance and staining reactions of vernix. It appeared to them that the greater and more prolonged the intrauterine asphyxia, with aspiration of the contents of the amniotic sac and resultant interference with later extrauterine respiration, the greater the size and number of membranes in the lungs.

And, finally, Farber and Wilson,³⁷ in an extensive study of human material and ingeniously conducted animal experiments, were able to establish definitely the nature and the pathogenesis of the hyaline membranes in the lungs. They found the hyaline membranes identical in influenzal pneumonia, in various types of pneumonia in infants and growing children and in the lungs of newborn infants after aspiration of the contents of the amniotic sac. These membranes stained from pink to red with hematoxylin and eosin and from salmon pink to red with phosphotungstic acid hematoxylin, contained varying amounts of fat and did not reveal fibrin when stained for this material.

When animals were forced to breathe an atmosphere of such low oxygen and high carbon dioxide content that marked dyspnea leading to death occurred, the alveolar spaces were filled with varying amounts of serum frequently pressed by the inspired air into membrane formation against the alveolar walls. Also, when a foreign substance, such as horse serum, india ink or fibrinopurulent exudate, was instilled into the trachea and vigorous artificial respiration (Drinker) instituted, characteristic membranes formed of the material could be found lining the alveolar walls. They therefore concluded that for the production of the characteristic hyaline membranes these factors were necessary: (1) material capable of taking the characteristic eosin stain; (2) air in the alveolar spaces, probably under greater than normal tension; (3) partial obstruction to the passage of the air by semifluid material in the air passages, and (4) dyspnea, which may be interpreted as violent inspiratory efforts to force air by this obstruction.

The hyaline membranes in the lungs in cases of acute rheumatic fever, observed by Coburn; by Masson, Riopelle and Martin; by Had-

36. Farber, S., and Sweet, L. K.: Amniotic Sac Contents in the Lungs of Infants, *Am. J. Dis. Child.* **42**:1372-1383 (Dec.) 1931.

37. Farber, S., and Wilson, J. L.: The Hyaline Membrane in the Lungs, *Arch. Path.* **14**:437-460 (Oct.) 1932.

field, and by us, must therefore be interpreted in the light of the studies just reviewed. Not only have the hyaline membranes been found in patients with influenzal or various other forms of pneumonia, in asphyxiated infants with aspirated contents of the amniotic sac and in experimental animals, but we have observed them also in the lungs in 1 case each of malignant nephrosclerosis with uremia and mild cardiac failure, metastatic carcinomatosis of the lung, Hodgkin's disease, lymphosarcomatosis and subacute bacterial endocarditis.

ARTERIAL LESIONS

The early lesions in the lungs in cases of acute rheumatic fever—alveolitis, engorgement of capillaries, edema, congestion and the deposition of the hyaline membrane along the respiratory ducts—strongly suggest an alteration in the vascular permeability, with resultant diapedesis of red blood cells and transudation of an albuminous fluid into the alveoli. Vascular damage elsewhere in the body has been demonstrated in cases of acute rheumatic fever—in the skin, brain, kidneys and abdominal viscera; of especial interest in this connection are the changes observed in the main pulmonary artery and in its branches and ramifications in the lung.

Paul³⁸ was the first to observe extensive lesions in the media, with Aschoff bodies in the adventitia, of the pulmonary artery in a case of acute rheumatic fever. Kugel and Epstein,³⁹ in 24 cases of active rheumatic fever, found severe lesions, consisting of diffuse cellular infiltration in the intimal and subintimal layers of the media, with marked disruption of the elastic media, in the pulmonary artery in 5 instances. Von Glahn and Pappenheimer⁴⁰ had previously demonstrated changes in the smaller branches of the pulmonary artery.

In our series of 45 cases of acute rheumatic fever we have observed various changes in the smaller pulmonary arteries, arterioles and capillaries. Interestingly enough, in the 14 cases of acute, rapidly fatal rheumatic fever in which death occurred during the initial attack, no important or significant lesions were seen in the branches of the pulmonary artery. Severe arteritis was observed in 4 of the remaining 31 cases of acute fatal rheumatic fever with one or more previous attacks and resultant valvular changes. The lesions were severe, with perivascular, adventitial and medial infiltration of polymorphonuclear and

38. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, *Arch. Path.* **3**:354 (Feb.) 1927.

39. Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, *Arch. Path.* **6**:247-262 (Aug.) 1928.

40. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* **2**:235-249, 1926.

mononuclear cells, destruction of the media and marked intimal infiltration and proliferation causing complete destruction of the vessels, which usually were the medium-sized arteries and arterioles. Otherwise, the usual vascular change in these cases was one of intimal proliferation (which progressed in many instances to complete obliteration of the lumen), distinct medial thickening and adventitial proliferation undergoing fibrinoid degeneration. Many of these medium-sized and smaller arteries and arterioles were occluded by thrombi. Occasionally the veins were seen to be thickened and hyperplastic.

HEPATIC EDEMA

In order to throw further light on the probability of capillary damage in rheumatic fever, we have studied the liver in all 45 cases of acute rheumatic fever, as well as in the control cases. Rössle⁴¹ has long looked on hepatic edema as the evidence of a toxic lesion of the capillary wall, which becomes permeable to plasma and suffers destruction and desquamation of its endothelium. Keschner and Klemperer⁴² found 79 instances of intrahepatic edema in a series of 505 unselected autopsies (15 per cent), and intrahepatic edema was detectable in 39 per cent of cases of cardiac failure. They failed to find any difference in the frequency of the edema between the cases of failure during rheumatic fever and those of failure due to vascular myocardial lesions. For this reason they accounted for the hepatic edema on a mechanical basis. However, their finding of hepatic edema in cases of malignant nephrosclerosis, influenza, diabetic coma, uremia and exophthalmic goiter, without coexistent cardiac failure, led them to believe that primary hepatic edema is of significance as the only morphologic evidence of increased permeability of the capillary wall.

We have studied the livers according to the method outlined by Keschner and Klemperer and have regarded as showing edema only those sections in which the capillary walls were separated from the liver cell cords and in which the distended pericapillary (Disse) spaces contained stained granular (protein) material. Mere separation of the capillary wall was not accepted as evidence of edema, since focal detachment alone could be demonstrated in almost every instance, and even widespread detachment was frequently apparent. This separation can also be accentuated by fixatives, especially by alcohol.

The incidence of intralobular hepatic edema in the 45 cases of acute fatal rheumatic fever was as follows: in the first group (14 cases of

41. Rössle, R.: Die Veränderungen der Blutkapillaren der Leber und ihre Bedeutung für die Histogenese der Lebercirrhose, *Virchows Arch. f. path. Anat.* **188**:484-527, 1907.

42. Keschner, H. W., and Klemperer, P.: Frequency and Significance of Hepatic Edema, *Arch. Path.* **22**:583-592 (Nov.) 1936.

initial acute fatal rheumatic fever with no previous rheumatic cardio-valvular disease) 11 times; in the second group (10 cases of acute rapidly fatal rheumatic fever with previous chronic rheumatic cardio-valvular disease) 8 times, and in the third group (21 cases of a more prolonged attack of fatal rheumatic fever with previous chronic cardio-valvular disease) 13 times. In 1 case in the last group severe arterial lesions, characterized by enormous intimal proliferation and striking periarterial fibrosis, were present in the liver. In all, intralobular hepatic edema was present in 32 of the 45 cases of acute rheumatic fever, or 71 per cent (79 per cent of the cases of rapidly fatal disease and 62 per cent of the cases of more prolonged disease). Contrast this with the finding of hepatic edema by Keschner and Klemperer in 39 per cent of all cases of cardiac insufficiency, both rheumatic and vascular in origin, and the finding of hyaline membranes in the respiratory bronchioles in 36 per cent of our cases of acute rheumatic fever. In all but 3 of the instances in which the hyaline bands occurred in the lungs intralobular hepatic edema also was present. The presence of intralobular hepatic edema in cases of acute rheumatic fever impresses us as further evidence of the generalized increased permeability of the capillary wall in this disease, and this generalized permeability affords an explanation for the alveolitis consisting mainly of the seroalbuminous extravasation into the alveolar tree and the formation of the hyaline membranes along the walls of the respiratory bronchioles.

SUMMARY AND CONCLUSIONS

A study has been presented of the observations at autopsy in the lungs in 45 consecutive cases of acute rheumatic fever, selected regardless of the presence or absence of any clinical and gross pathologic pulmonary changes. Such a selection has enabled us to reconstruct the chronologic sequence of events in the development of the pathologic process in the lung from the purely microscopic stage, in which no clinical signs could have occurred, to the stage at which pulmonary damage is clinically manifest.

We were fortunate in having an opportunity to study 14 cases of acute rheumatic fever, fatal in the initial attack, in which chronic cardio-valvular disease with chronic stasis in the lungs was absent. In some instances the entire course of illness lasted only a few days, which enabled us to observe the earliest changes possible in the lungs during acute rheumatic fever. In addition, 31 cases of acute rheumatic fever were studied in which one or more previous attacks had resulted in antecedent cardiovalvular disease with anatomic valvular changes. Here we had an opportunity to study the combination of the effects of previous pulmonary stasis secondary to chronic valvular disease and the immediate effects of the acute and fatal attack.

From the examination of these 45 cases of acute fatal rheumatic fever we believe that the pulmonary changes can be chronologically tabulated thus:

The first stage consists of passage of considerable fluid into the alveoli, septums and interlobular spaces, with marked congestion of alveolar capillaries, engorgement and diapedesis of erythrocytes, together with desquamation of large mononuclear cells into the alveoli. This alveolitis is nonfibrinous and nonbacterial and strongly suggests alterations in the capillaries, with resultant increased permeability and diapedesis of erythrocytes and transudation of albuminous fluid into the alveoli. Hyaline membranes are formed in the respiratory bronchioles and the alveolar ducts in about 50 per cent of the cases.

As the disease is prolonged this stage is followed by thickening and infiltration of the interlobular septums with mononuclear cells, with resultant fibrosis and organization. The smaller arteries show occasional thickening. Gross examination of the lungs at this stage reveals many patchy foci of dark red, fleshy, noncrepitant, nonaerated areas, which have a peculiar india rubber consistency. This stage has been observed in the 14 cases in which death was due to the initial attack of rheumatic fever and in which no previous valvular disease had existed.

In all the remaining cases evidence of previous cardiovalvular disease with resultant pulmonary congestion was found, with the familiar effects of more or less long-standing stasis. But in many cases, in addition to the chronic stasis engendered by the previous attacks, we also observed the evolution of an acute stage similar to that described for the cases of fatal initial attack. And in 9 cases typical hyaline membranes were seen. No Aschoff bodies were found in the lungs in any of the 45 cases.

Twenty cases of chronic rheumatic cardiovalvular disease, mitral stenosis, in which the patient died of intercurrent disease or of chronic heart failure without evidences of rheumatic fever; 23 cases of coronary arterial disease in which the patient died of heart failure, and 16 cases of hypertensive heart disease, with failure, were similarly studied to consider the possibility that the pulmonary lesions seen in cases of acute rheumatic fever were a result of the pulmonary stasis of congestive heart disease. In none of the control cases was a picture observed which approached in similarity that seen in cases of acute fatal rheumatic fever.

The mechanism of the formation of the hyaline membranes in the lungs is dependent on the following factors (and not on any specific infection, such as rheumatic fever or influenza, as had been previously believed): (1) material capable of taking the characteristic eosin stain; (2) air in the alveolar spaces, probably under greater than normal

tension; (3) partial obstruction to the passage of the air by semifluid material in the air passages, and (4) dyspnea, which may be interpreted as violent inspiratory efforts to force air by this obstruction.

The alveolitis and the formation of hyaline membranes are in our opinion a result of an alteration in vascular permeability, with resultant diapedesis of erythrocytes and transudation of seroalbuminous fluid from the capillaries into the alveoli. This vascular damage has been found in cases of rheumatic fever in various other organs of the body. We have seen involvement of the main pulmonary artery and also, in several instances, severe inflammatory arteritis of the various branches of the pulmonary artery in the lungs in the cases presented.

As further evidence of the tendency to vascular damage in rheumatic fever, resulting in increased permeability of the capillary wall, we have found intralobular hepatic edema in 71 per cent of the 45 cases of acute fatal rheumatic fever.

In conclusion, we believe that:

1. A specific rheumatic lung or rheumatic pneumonia cannot be considered to exist. Aschoff bodies were not found in a single instance.

2. A characteristic, though not specific, pulmonary picture is present, which consists of alveolitis, marked congestion, edema, engorgement and the formation of hyaline membranes.

3. These lesions are considered to be a result of damage to the capillaries, with resultant alterations in vascular permeability.

4. Vascular damage was likewise present in the main pulmonary artery and its branches and in the hepatic capillaries.

5. This vascular change corresponds to the involvement seen in the arterial tree in various organs of the body in acute rheumatic fever.

TUBERCULOMA OF HYPOPHYSIS WITH INSUFFICIENCY OF ANTERIOR LOBE

A CLINICAL AND PATHOLOGIC STUDY OF TWO CASES

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CHICAGO

As early as 1844 von Rokitsansky¹ noted the rarity of tubercles in the hypophysis. Both Anderson² and Scott and Graves³ (in a review of the literature to 1933) found no recorded cases of tuberculoma of the hypophysis in the literature. Certain authors⁴ failed to mention the existence of tuberculous involvement of this endocrine gland, while others⁵ concurred in the opinion that it was rare. Garland and Armitage,⁶ in examining 3,533 brains post mortem, found that only 2 of 89 intracranial tuberculomas involved the sella turcica. Falta⁷ mentioned that von Frankl-Hochwart found 7 instances of a tubercle in 97 cases of tumor

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1. von Rokitsansky, C.: *Handbuch der speziellen pathologischen Anatomie*, Vienna, Braumüller & Seidel, 1844, vol. 1; cited by Kraus.¹⁰

2. Anderson, F. N.: Tuberculoma of the Central Nervous System, *Arch. Neurol. & Psychiat.* **20**:354 (Aug.) 1928.

3. Scott, E., and Graves, G. O.: Tuberculomas of the Brain, *Am. Rev. Tuberc.* **27**:171 (Feb.) 1933.

4. Courville, C. B.: *Pathology of the Central Nervous System*, Mountain View, Calif., Pacific Press Publishing Association, 1937. Frazier, C. H.: Review, Clinical and Pathological, of Parahypophyseal Lesions, *Surg., Gynec. & Obst.* **62**:1 (Jan.); 158 (Feb.) 1936.

5. Davidoff, L. M.: Diagnosis of Tumors in and Around the Pituitary Gland, *New York State J. Med.* **36**:1610 (Nov. 1) 1936. Van Wagenen, W. P.: Tuberculoma of the Brain, *Arch. Neurol. & Psychiat.* **17**:57 (Jan.) 1927. Schidrowsky, P.: Zur Frage der Tuberkulome des zentralen Nervensystems, *Arch. f. klin. Chir.* **155**:703, 1929. Bucy, P. C.: The Hypophysis Cerebri, in Penfield, W.: *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, vol. 2.

6. Garland, H. G., and Armitage, G.: Intracranial Tuberculoma, *J. Path. & Bact.* **37**:461 (Nov.) 1933.

7. Falta, W.: *Endocrine Disease*, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1923.

of the hypophysis without acromegaly. Houssay⁸ stated that "circumscribed tuberculous lesions affecting the pituitary as well as metastatic lesions from distant foci and invasion from neighboring tissues have been described," and listed twenty-one references to the literature. Simonds⁹ was able to collect records of 28 instances of tuberculous invasion of the pituitary gland, in 10 of which the disease was miliary, while in the rest the tubercles were conglomerate. A similar review was later published by Kraus.¹⁰ Riecker and Curtis,¹¹ in a review of the autopsies in 24 cases of Simmonds' disease, reported tuberculosis as the destructive agent in 2 instances. Kurzak¹² found 32 cases of tuberculous disease of the hypophysis. More recently Berblinger¹³ described the necropsy observations in the case of a 52 year old woman with hypophysial tuberculosis, with an excellent review of the subject. We have encountered 2 cases of tuberculosis of the anterior lobe producing symptoms of pituitary insufficiency among 14,160 autopsies performed by members of the department of pathology of the Cook County Hospital from 1929 to 1940 inclusive. Among these there were 652 cases of various types of pulmonary tuberculosis and 368 cases of tuberculous meningitis; in none of the latter was there hypophysial involvement.

REPORT OF CASES

CASE 1.—S. J., a white woman aged 37, gave a history of amenorrhea, marked asthenia, severe headaches accompanied by nausea and vomiting and a loss of 50 pounds (22.7 Kg.) of weight in seven months. She had been treated with some form of glandular material by injection for the absence of menstruation, with no effect. She had one living child, of a normal pregnancy and an uneventful puerperium; she had had no miscarriages. There was nothing of significance in her past or family history.

Examination revealed she was undernourished and apathetic, with a blood pressure, expressed in millimeters of mercury, of 70 systolic and 50 diastolic. She weighed 109 pounds (49.4 Kg.). Her skin and hair were dry, and the former was scaly; the eyegrounds showed blurring of the margin of the right disk, and

8. Houssay, B. A.: Hypophysis and Resistance to Intoxications, Infections and Tumors, *New England J. Med.* **214**:1128 (June 4) 1936.

9. Simonds, J. P.: Tuberculosis of the Hypophysis, in Barker, L. F., and others: *Endocrinology and Metabolism*, New York, D. Appleton and Company, 1922, vol. 1.

10. Kraus, E. J.: Die Hypophyse, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8.

11. Riecker, H. H., and Curtis, A. C.: Hypophyseal Cachexia (Simmonds' Disease), *J. A. M. A.* **99**:110 (July 9) 1932.

12. Kurzak, H.: Die Tuberkulose des Keilbeins und ihre Beziehungen zur Hypophyse, *Ztschr. f. Tuberk.* **34**:433, 1921.

13. Berblinger, W.: Hypophysentuberkulose als Todesursache, *Schweiz. med. Wchnschr.* **69**:1217 (Dec. 2) 1939.

the left fundus was normal. The fields of vision were not determined. The breasts were flat and atrophic. No other abnormalities were noted.

Laboratory studies gave the following results: urine, normal; hemoglobin concentration, 89 per cent (Sahli); red cell count, 5,720,000 per cubic millimeter; white cell count, 11,400 per cubic millimeter, with 53 per cent neutrophils, 2 per cent eosinophils, 2 per cent basophils, 39 per cent lymphocytes and 4 per cent monocytes. The Wassermann and Kahn reactions of the blood were negative. The basal metabolic rate varied from -21 to -29 per cent. Chemical studies of the blood yielded information as follows (values are expressed in milligrams per hundred cubic centimeters of serum or plasma): calcium, 9.21; phosphorus,

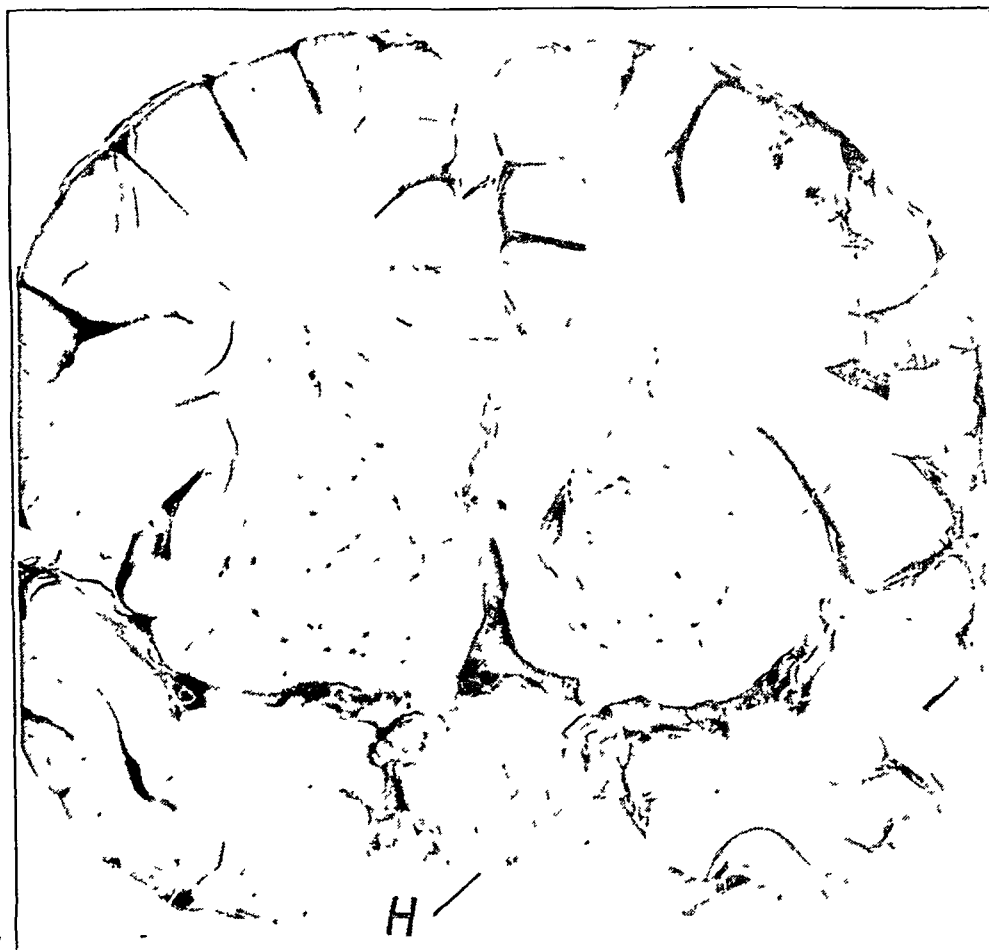


Fig. 1 (case 1).—The hypophysis (*H*) is attached to the brain. Note the marked enlargement of the anterior lobe and its similarity to a tumor.

4.00; nonprotein nitrogen, 44.00; uric acid, 5.5, and sodium, 345.00 (normal 330.00). An oral dextrose tolerance test showed a fasting value of 79 mg. per hundred cubic centimeters, and after ingestion of 100 Gm. of dextrose the values at one hour intervals were 115, 93 and 70 mg. per hundred cubic centimeters of venous blood. Roentgenologic studies showed increased hilar markings in the lungs, thickening of the right apical pleura and a sella turcica of normal size, with no erosion of the clinoid processes of the sphenoid bone.

The diagnosis was insufficiency of the anterior lobe of the pituitary of undetermined origin. Treatment during the diagnostic period consisted of a high vitamin, high calory diet, on which the patient gained 10 pounds (4.5 Kg.).

Before more specific therapy was started, the patient suddenly fainted and died, after a short period of Cheyne-Stokes respiration.

Necropsy (performed by J. D. K.).—The right pleural cavity was partially obliterated by dense fibrous adhesions. An area of healed fibroindurative tuberculosis was present in the apex of the right lung. The thyroid gland was small and weighed 8.5 Gm. The two adrenal glands weighed 18 Gm. The uterus measured 7 by 5.5 by 2.5 cm.; its wall was firm and 16 mm. thick. The endometrium was smooth and contained a single flat polyp, 5 mm. in length, and a firm subserous nodule, 2 mm. in diameter. The oviducts were thin walled and

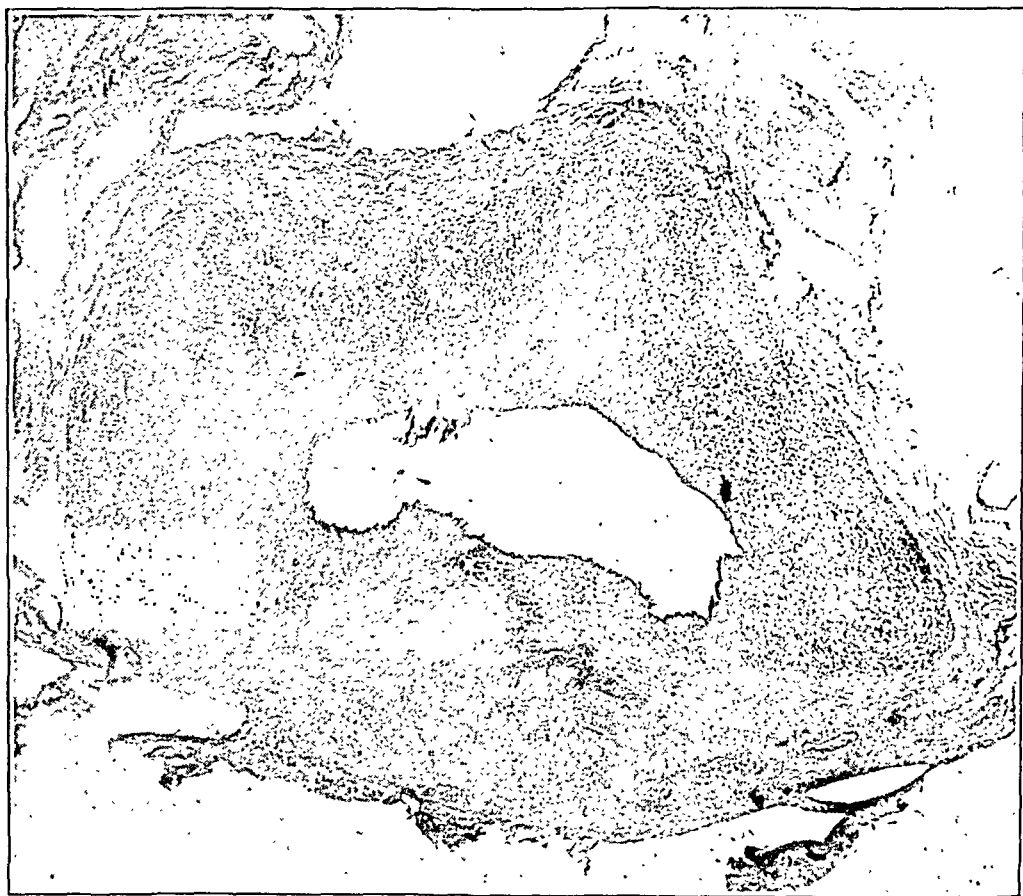


Fig. 2 (case 1).—The anterior lobe of the hypophysis (low magnification). Note the central area of caseation necrosis.

patent. Each ovary measured 35 by 18 by 10 mm., and the left one contained a single follicular cyst, 12 mm. in diameter. The anterior lobe of the hypophysis was transformed into a tumor mass measuring 30 mm. in transverse diameter, 17 mm. in anteroposterior diameter and 12 mm. in vertical diameter (fig. 1).

The optic nerves were slightly compressed. The cut surface of the tumor appeared light grayish white, mottled with single and confluent light yellow areas, which occupied about two thirds of the surface of the section.

Microscopic Examination.—The tumor was a tuberculoma, replacing most of the anterior lobe of the hypophysis and leaving only a narrow rim of intact acini in the periphery (fig. 2). The central portion of the tuberculoma showed areas of caseation necrosis, which in turn were surrounded by a zone of fibrillar and

hyaline connective tissue, often interrupted by groups of plasma cells, eosinophils, leukocytes, lymphocytes and large mononuclear cells. Scattered about were single typical Langhans giant cells and nests of epithelioid cells (fig. 3). The intact peripheral zone of hypophyseal tissue showed a preponderance of eosinophilic cells (fig. 4). The capsule was extremely thickened and showed marked fibrosis, with foci of plasma cells, lymphocytes and polymorphonuclear leukocytes. The stalk showed similar infiltrations with single giant cells. The posterior lobe was

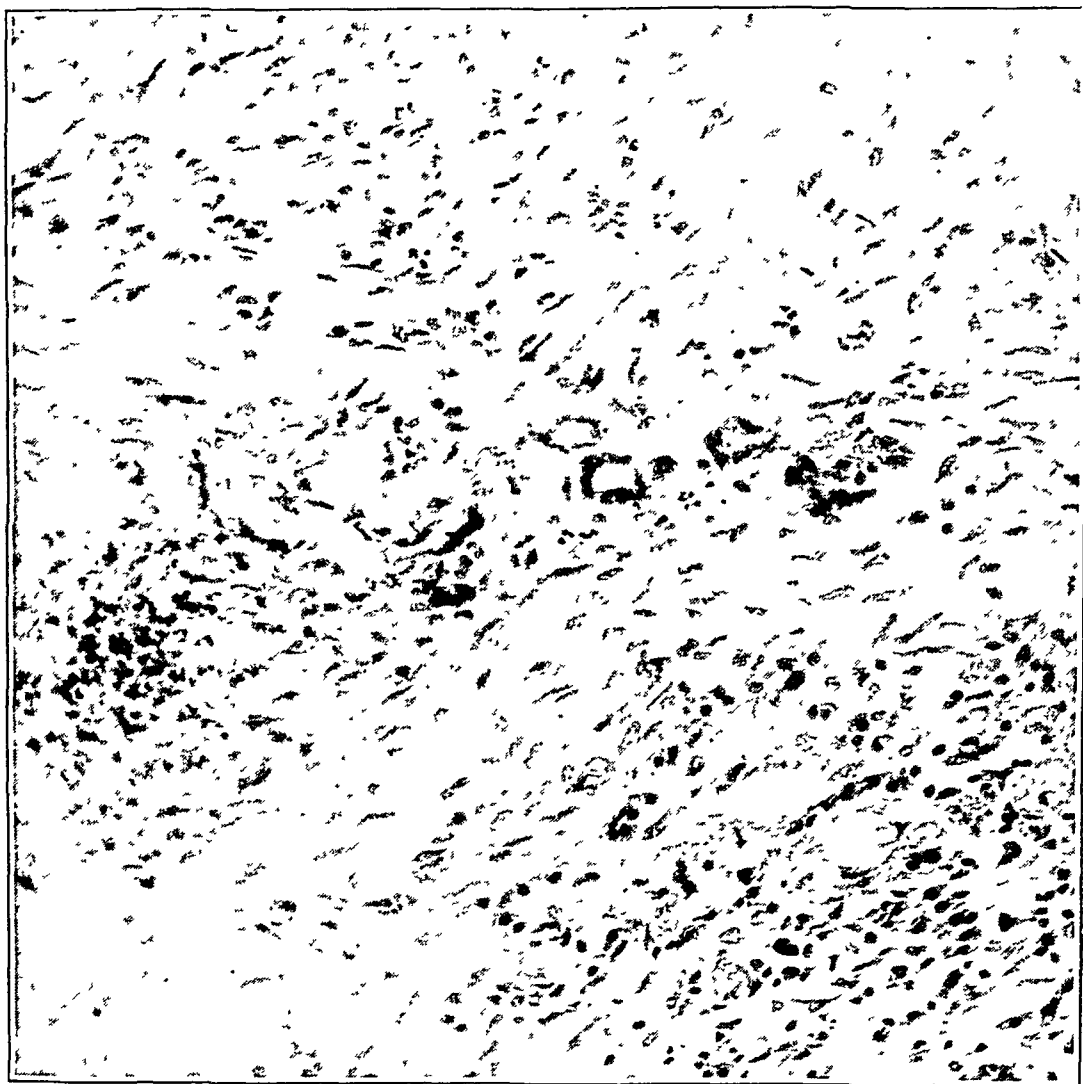


Fig. 3 (case 1).—A photomicrograph of the periphery of the tuberculoma taken under high magnification, showing several giant cells of Langhans and extensive fibrosis.

intact and normal. No tubercle bacilli were seen in sections stained after the Ziehl-Neelsen method.

Anatomic Diagnosis.—The diagnosis made at autopsy was caseous tuberculosis (tuberculoma) of the anterior lobe of the pituitary gland with extension into the stalk, hypoplasia of the thyroid gland, healed fibroindurative tuberculosis of the apex of the upper lobe of the right lung, fibrous obliteration of the pleural cavity, marked edema of the brain, fatty degeneration of the liver, parenchymatous degeneration of the myocardium and the kidneys, endometrial polyp and pronounced emaciation.

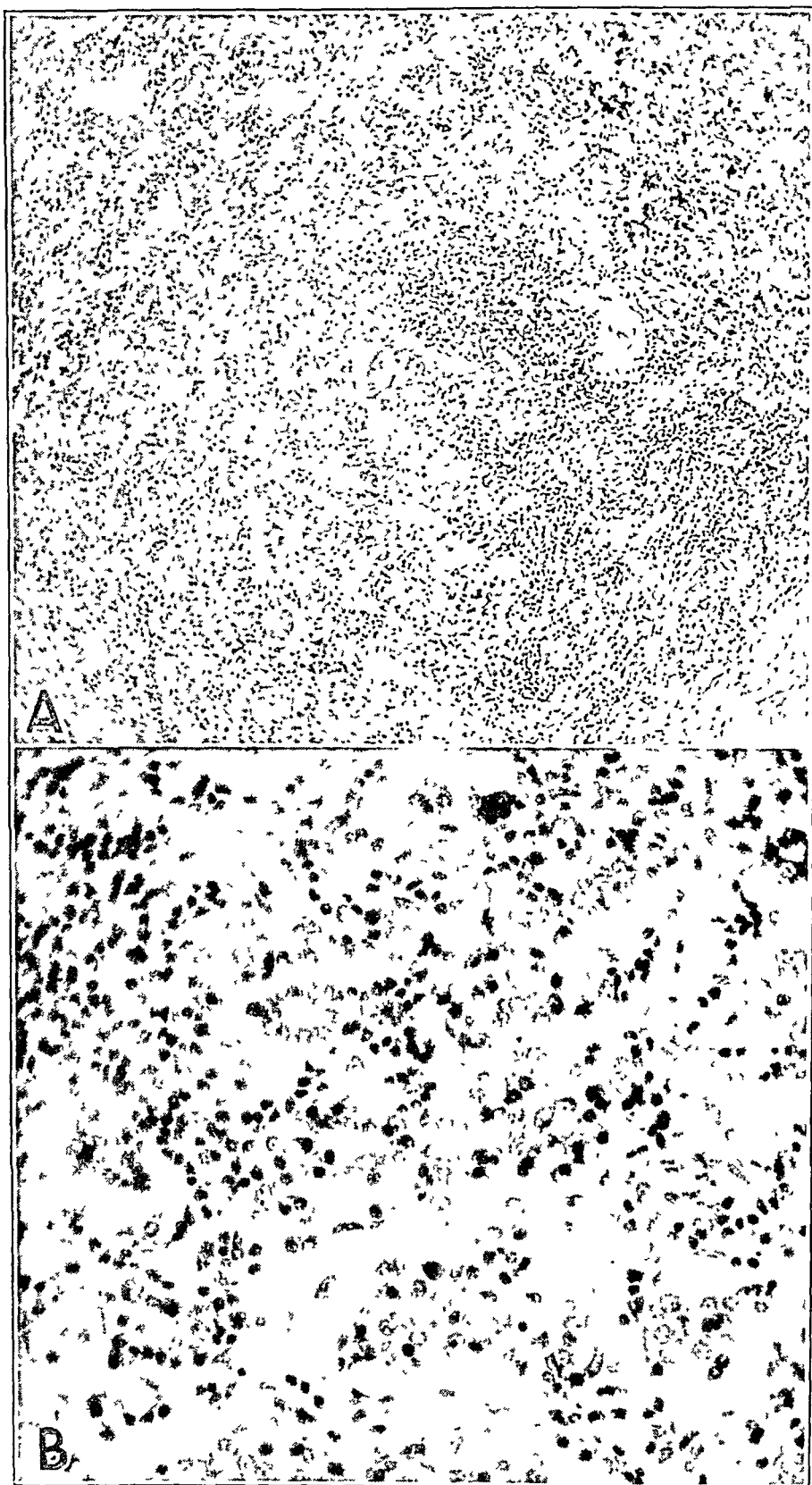


Figure 4

(See legend on opposite page)

CASE 2.—P. M. was a white man aged 44. According to a history obtained from his sister, his vision and hearing had begun to fail thirty years before his admission to the hospital. Gradually the loss increased, so that for the past eight years he had been totally blind and deaf. For three years he had suffered from severe dizzy spells, with increasing difficulty in walking, and for two years he had been completely bedridden. Except for pneumonia in childhood, he had had no significant past illness.

On examination he did not appear acutely ill. His skin was smooth, dry and yellowish, and his hair was dry and tough. His blood pressure, measured in millimeters of mercury, was 80 systolic and 60 diastolic. He showed practically no response to either light or sound. Examination of the eyes revealed clouding of the lens and scleral irregularities. The hair of the face and pubic region was thin and scanty. The penis was small, and the right testis was undescended. Also the musculature was generally flaccid, and the anterior and posterior cervical lymph nodes were involved on both sides. Blood counts showed 4,450,000 red corpuscles and 9,600 white corpuscles per cubic millimeter, with 51 per cent neutrophils, 42 per cent lymphocytes and 7 per cent eosinophils. The hemoglobin concentration (Sahli) was 81 per cent. Analysis of the gastric contents showed nothing abnormal. No albumin or sugar was found in the urine. A dextrose tolerance test showed a fasting blood sugar value of 60 mg. per hundred cubic centimeters, and after 100 Gm. of dextrose was administered orally, the blood sugar values, determined at hourly intervals, were 107, 120, 140 and 148 mg. per hundred cubic centimeters of venous blood. The Kahn and Wassermann reactions both of blood and of spinal fluid were negative. Roentgen examination of the chest and the sella turcica showed no abnormality. The patient could not cooperate for determination of the basal metabolic rate. No definite etiologic diagnosis was made, although hypopituitarism was considered as one of the possibilities. The patient vegetated in the hospital for several months and died from what was thought to be terminal bronchopneumonia.

Necropsy (performed by Dr. R. H. Jaffé).—The two adrenal glands weighed 11 Gm. and had narrow cortices. The thyroid weighed 10 Gm. and appeared light purple-gray and uniformly granular. The hypophysis measured 9 by 8 by 6 mm. and was soft in consistency. Permission to remove the eyes for examination was not given.

Microscopic Examination.—The adrenal cortex was narrow and consisted mainly of zona glomerulosa and pigmented zona reticularis. Of the zona fasciculata there was left only an occasional adenoma-like rest, composed of polygonal cells with ample, finely granular cytoplasm. The adrenal medulla was well preserved. The thyroid gland consisted of medium-sized, colloid-filled follicles with a flat epithelial lining; there were many interstitial lymph nodules centered about congested capillaries. The seminiferous tubules of the testes were largely atrophic and were separated by an increased amount of stroma; the basement membrane was thickened. In a few single tubules there were active proliferation and for-

EXPLANATION OF FIGURE 4

Photomicrographs under high magnification of areas in the periphery of the tuberculoma (case 1), from the section shown in figure 2. Note (A) the extensive replacement of the acinar structure by tuberculous granulation tissue and (B) the remnants of widely separated acini in the periphery of the anterior lobe.

mation of mature spermatozoa. No definite interstitial cells were identified. The posterior lobe of the hypophysis was intact. The anterior lobe was completely replaced by dense connective tissue with scanty, deeply stained nuclei. In places the connective tissue was infiltrated with small round cells of lymphocytic type and single larger histiocytes. Here and there giant cells of Langhans type with peripheral oval nuclei were noted, as well as an occasional small group of epithelioid cells with ample cytoplasm. No tubercle bacilli were found in sections stained by the Ziehl-Neelsen method. In methylene blue-stained sections were a few cuboidal cells with frayed borders and oval nuclei, the cytoplasm of which contained vacuoles and coarse, deep blue granules.

The cuboidal cells were distinctly different from the mast cells, which had a purple-red, metachromatic granulation. Blood vessels of capillary type were scanty; in sections stained for elastic tissue the sclerosed areas were found to be devoid of elastic fibrils. The small arteries and veins near the sclerosed areas were unchanged. Although sections were taken at many different levels, no intact parenchyma could be detected. Sections of the brain from the subthalamic region, the infundibulum, the optic chiasm and the lentiform nucleus revealed nothing abnormal except slight thickening of the walls of smaller arteries and congestion of the capillaries.

Anatomic Diagnosis.—The diagnosis made at necropsy included sclerosed tuberculoma of the anterior lobe of the pituitary gland, female distribution of body hair, atrophy of the adrenal cortex and fibrocaceous tuberculous primary complex in the lower lobe of the right lung.

COMMENT

Our first case fulfils the criteria of pituitary cachexia (Simmonds' disease), with the clinical syndrome of amenorrhea, severe asthenia, marked and rapid loss of weight with cachexia, hypotension, dryness of the skin and hair, low basal metabolic rate and high dextrose tolerance. The picture is completed by the pathologic findings of complete destruction of the anterior lobe of the hypophysis by a tuberculous lesion, with evidence of chronic pulmonary tuberculosis and hypoplasia of the thyroid. The absence of adrenal cortical atrophy is consistent with a diagnosis of Simmonds' disease, according to Silver.¹⁴

In our second case, although such clinical symptoms of pituitary failure as eunuchoid body build with female distribution of hair and hypotension were present, we observed an old sclerosed tuberculoma of the anterior lobe, with atrophy of the zona fasciculata of the adrenal cortex and possibly the results of pressure on the seventh cranial nerve and the optic chiasm.

Although hypofunction of the pituitary gland was suspected clinically, particularly in the first case, and rediagnosed, tuberculosis as the etiologic factor was not suspected in either case, because of its rarity.

14. Silver, S.: Simmonds' Disease (Cachexia Hypophyseopriva), Arch. Int. Med. 51:175 (Feb.) 1933.

As described by Simonds⁹ and Berblinger,¹³ the pathologic picture of tuberculosis of the hypophysis may be associated with, or secondary to, the following conditions: (1) an acute miliary spread of the disease, (2) nearby meningitis or osteomyelitis of the sphenoid bones or (3) a hematogenous metastasis, with formation of large but slow-growing conglomerate tubercles. The first two forms, which are acute, run a rapid course and usually terminate in early death; they do not progress to produce local symptoms, or if symptoms are present they are overshadowed by the general picture of the causative syndrome. The third form, however, can produce various syndromes as a result of pressure on the pituitary gland and on surrounding important structures, as would any other lesion in the same area. Both cases are probably examples of early miliary generalized tuberculosis (according to Ranke's classification), with latent exacerbation in the hypophysis and no activity in the lungs.

Simonds⁹ stated, "Tuberculosis of the hypophysis is only rarely associated with symptoms referable to that gland, although in many of the recorded cases, clinical data are very imperfectly reported." However, depending on the exact site of the lesion, its size, rate and direction of growth and the age at which the patient is affected, many varied syndromes (according to Berblinger¹³) can be produced.

The lesion may result in the manifestations of any nonspecific expanding lesion in this area of the brain, such as paralysis of the abducens or the oculomotor nerve, bitemporal hemianopia or amaurosis resulting from compression of the seventh nerve. Thus, blindness occurred in cases reported by Boyce and Beadles¹⁵ and by Beck,¹⁶ as well as in our second case. Recently Coleman and Meredith¹⁷ described a case of diffuse tuberculosis of the pituitary gland, associated with enlargement of the sella turcica, primary atrophy of the optic nerve and bitemporal hemianopia, in which the growth simulated a tumor. They were able to remove the mass surgically, with complete recovery from the visual defects and no evidence of recurrence at the end of three and a half years.

Also the clinical syndrome of adiposogenital dystrophy (Fröhlich's) can be produced from involvement of the diencephalon or the hypothalamus, as described by Kraus.¹⁸

15. Boyce, R., and Beadles, C. F.: A Further Contribution to the Study of the Pathology of the Hypophysis Cerebri, *J. Path. & Bact.* **1**:359, 1892.

16. Beck: Tuberkulöse Entartung des Hirnanhanges als Ursache der Diplopie und des Strabismus, *Ztschr. f. Ophth.* **4**:401, 1835; cited by Heidkamp, H.: Beitrag zu Tuberkulose der Hypophyse, *Virchows Arch. f. path. Anat.* **210**:445, 1912.

17. Coleman, C. C., and Meredith, J. M.: Diffuse Tuberculosis of the Pituitary Gland Simulating Tumor with Postoperative Recovery, *Arch. Neurol. & Psychiat.* **44**:1076 (Nov.) 1940.

18. Kraus, E. J.: Zur Pathogenese der Dystrophia adiposogenitalis, *Med. Klin.* **20**:1290 (Sept. 14) 1924.

If the neurohypophysis is attacked diabetes insipidus or polyuria may result, as noted in 4 of Simmonds' ⁹ cases.

Pituitary cachexia, or Simmonds' disease, due to a destructive lesion of the glandular parenchyma of the anterior lobe, is only rarely caused by tuberculosis. Simmonds ¹⁹ expressed the opinion that tuberculosis was an infrequent cause of the syndrome named after him. Silver, ¹⁴ in a review of 42 cases of Simmonds' disease in which the diagnosis was confirmed by necropsy, mentioned the report of Schlagenhafer ²⁰ and that of Budde ²¹; in the latter multiple areas of necrosis, resulting either from tuberculosis or syphilis, were described. Our first case and those reported by Schlagenhafer ²⁰ and Berblinger, ¹³ and possibly those reported by Froboese, ²² Knoll ²³ and Schneider ²⁴ (no autopsy), are examples of Simmonds' disease caused by tuberculosis of the pituitary gland.

SUMMARY

Two cases of tuberculoma of the hypophysis with autopsy are reported, 1 with the clinical picture of pituitary cachexia and the other with associated eunuchoidism, blindness and deafness.

Tuberculosis of the hypophysis is rare.

The hypophysis may be involved in one of three ways: (a) acute miliary spread of the disease, (b) extension from contiguous basilar meningitis or sphenoid osteomyelitis or (c) hematogenous dissemination with latent exacerbation producing conglomerate tubercles.

Symptoms referable to the hypophysis are not usually associated with the first two types, while in the hematogenous form the symptoms depend on the part of the gland and the surrounding structures involved.

Pituitary cachexia (Simmonds' disease) is rarely due to the destructive effect of tuberculosis, since there are reports of probably only 3 authentic cases, including ours, and 3 more doubtful ones.

19. Simmonds, M.: Ueber Tuberkulose der Hypophysis, *Zentralbl. f. allg. Path. u. path. Anat.* **25**:194 (Feb.) 1914.

20. Schlagenhafer: Zur Kachexie hypophysären Ursprungs, *Virchows Arch. f. path. Anat.* **222**:249, 1916.

21. Budde, M.: Zur Kenntnis der bösartigen Hypophysengeschwülste und hypophysären Kachexie, *Frankfurt. Ztschr. f. Path.* **25**:16, 1921.

22. Froboese, C.: Die tuberkulöse Erkrankung der Hypophysis, insbesondere über die primäre Form, *Zentralbl. f. allg. Path. u. path. Anat.* **29**:145 (March) 1918.

23. Knoll, W.: Beitrag zum Bilde der hypophysären Kachexie, *Wien. Arch. f. inn. Med.* **4**:555, 1922.

24. Schneider, H.: Kachexie bei wahrscheinlich fort geleiteter Hypophysentuberkulose, *Wien. med. Wchnschr.* **72**:233 (Jan. 28) 1922.

METABOLISM IN ORGANIC HYPERINSULINISM

II. EFFECTS OF EPINEPHRINE ON GLYCEMIC LEVEL AND ON COMBUSTION OF CARBOHYDRATE

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The effects of the administration of epinephrine on the metabolism of carbohydrate in normal human subjects and in normal animals have been studied extensively.¹ With regard to the specific effect of epinephrine on total combustion of carbohydrate in the normal organism there is great disagreement. Colwell and Bright,^{1f} using normal intact animals, showed that the slow, continuous infusion of a solution of

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1. (a) Cori, C. F., and Cori, G. T.: Mechanism of Epinephrine Action: Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, *J. Biol. Chem.* **79**:309, 1928; (b) Mechanism of Epinephrine Action: Influence of Epinephrine and Insulin on Carbohydrate Metabolism of Rats in Postabsorptive State, *ibid.* **79**:321, 1928; (c) Mechanism of Epinephrine Action: Influence of Epinephrine on Utilization of Absorbed Glucose, *ibid.* **79**:343, 1928; (d) Mechanism of Epinephrine Action: Influence of Epinephrine on Lactic Acid Production and Blood Sugar Utilization, *ibid.* **84**:683, 1929. (e) Cori, C. F.; Fisher, R. E., and Cori, G. T.: Effect of Epinephrine on Arterial and Venous Plasma Sugar and Blood Flow in Dogs and Cats, *Am. J. Physiol.* **114**:53, 1935. (f) Colwell, A. R., and Bright, E. M.: Use of Constant Glucose Injections for Study of Induced Variations in Carbohydrate Metabolism: Suppression of Glucose Combustion by Continuous Prolonged Epinephrine Administration, *ibid.* **92**:555, 1930. (g) Bridge, E. M., and Noltie, H. R.: Action of Adrenalin on Respiratory Quotient, *J. Physiol.* **85**:334, 1935. (h) Soskin, S.; Priest, W. S., and Schutz, W. J.: Influence of Epinephrine upon Exchange of Sugar Between Blood and Muscle, *Am. J. Physiol.* **108**:107, 1934. (i) Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: Comparative Influence of Epinephrine and of Dextrose on Utilization of Sugar by Muscles, Determined with the Aid of Thermoströmuhr Measurements of Blood Flow, *ibid.* **118**:328, 1937. (j) Himsworth, H. P., and Scott, D. B. M.: Action of Adrenalin in Accelerating Removal of Blood Sugar by Peripheral Tissues, *J. Physiol.* **93**:159, 1938. (k) Conn, J. W.; Conn, E. S., and Johnston, M. W.: Effects of Alimentary and Adrenalin Hyperglycemia upon Total Oxidation of Glucose in Normal Humans, *J. Nutrition* **19** (supp.):16, 1940.

epinephrine hydrochloride resulted in complete suppression of carbohydrate combustion, as indicated by the respiratory gaseous exchange, despite the fact that a continuous, excessive supply of dextrose was being simultaneously infused. They found further that when the nonprotein respiratory quotient reached the level interpreted as indicating exclusive combustion of fat, the recovery of urinary dextrose equaled the intravenous supply and that the cessation of infusion of a solution of epinephrine hydrochloride resulted in diminishing glycosuria, a rising respiratory quotient, diminishing urinary excretion of nitrogen and deposition of glycogen in the liver and in muscle. Cori and his co-workers² elaborated these experiments and arrived at similar conclusions. Soskin and his associates,³ denying the validity of the respiratory quotient as an index of carbohydrate combustion, used other methods for gathering their data. Careful measurements of blood flow through the muscles and of simultaneous arteriovenous differences in blood sugar indicated normal utilization of carbohydrate by the tissues during continuous administration of epinephrine hydrochloride. Hims-worth and Scott^{1j} found that when the liver was suddenly excluded from the circulation the blood sugar level fell more rapidly if epinephrine hydrochloride was administered. This they interpreted as an accelerating effect of epinephrine on the removal of blood sugar by the peripheral tissues. Thus, depending on the method of investigation, results in animals have indicated (1) that epinephrine does not affect the utilization of carbohydrate by the tissues, (2) that it is capable of suppressing completely the oxidation of carbohydrate in the organism and (3) that it actually increases the rate of utilization of carbohydrate by the tissues. Results^{1k} previously reported by us with an associate suggested that in normal human subjects a single injection of a solution of epinephrine hydrochloride either had no effect on or caused mild suppression of the rate of combustion of carbohydrate.

Soskin and Levine⁴ presented evidence interpreted as indicating a relation between the rate of carbohydrate utilization and the height of the blood sugar level. The data were obtained from determinations of blood sugar, blood lactic acid and muscle glycogen made on eviscerated dogs. With an associate we^{1k} reported that a large rise of the blood sugar level produced in normal human subjects by the administration of epinephrine hydrochloride did not increase the combustion of carbohydrate. If anything, epinephrine decreased the rate of combustion of

2. Cori and others (footnotes 1 *b*, *c* and *e*).

3. Soskin, Priest and Schutz.^{1h} Soskin, Essex, Herrick and Mann.¹ⁱ

4. Soskin, S., and Levine, R.: Relationship Between Blood Sugar Level and Rate of Sugar Utilization, Affecting Theories of Diabetes, *Am. J. Physiol.* **120**: 761, 1937.

carbohydrate, despite the plethora of circulating blood sugar. On the other hand, a comparable rise in blood sugar produced by the ingestion of dextrose resulted in a marked increase in the rate of carbohydrate combustion. When dextrose and epinephrine were administered simultaneously, despite a tremendous elevation of the blood sugar the same results were obtained as when dextrose alone was given. We concluded, therefore, that the height per se of the blood sugar level does not control the rate of combustion of carbohydrate in the normal human being.

Studies on organic hyperinsulinism afford an unusual opportunity to clarify some of the points in question. The first point involves the validity of the method of indirect calorimetric determination of the rate of combustion of carbohydrate. We have shown by this method⁵ that in a case of organic hyperinsulinism evidence of tremendous overcombustion of carbohydrate can be obtained repeatedly, that the spontaneous hypoglycemia observed is due for the most part to this abnormality of metabolism and that the surgical removal of pancreatic islet cell tumors results in return of the normal rate of carbohydrate combustion, as determined by this method, and in disappearance of the hypoglycemic state. Under the conditions of the experiments described it is difficult to interpret in any other way the respiratory quotients obtained.

The second point on which studies on organic hyperinsulinism shed light is the question of hyperglycemia as the stimulus for increasing the rate of combustion of carbohydrate. Early in the development of dietetic therapy for hyperinsulinism it was suggested that the postprandial rise of the blood sugar, associated with the ingestion of a high carbohydrate meal, stimulated a secondary excessive removal of sugar from the blood and resulted, two to five hours later, in a severe hypoglycemic episode. It became customary, therefore, to use diets low in carbohydrate in an attempt to prevent the postprandial rise of blood sugar, with its subsequent secondary fall. The clinical success resulting from measures designed to minimize postabsorptive hyperglycemia⁶ seemed to indicate that patients with this condition were extremely sensitive to such stimulus. We showed⁵ that in a case of organic hyperinsulinism tremendous overcombustion of carbohydrate results from the ingestion of a standard dose of carbohydrate under controlled conditions. Thus, organic hyperinsulinism represents, among other things, a condition of

5. Conn, J. W., and Conn, E. S.: Metabolism in Organic Hyperinsulinism: I. Quantitative Studies of the Variations in the Rate of Combustion of Carbohydrate Produced by Alterations in the Diet, *Arch. Int. Med.* **68**:876 (Nov.) 1941.

6. Waters, W. C., Jr.: Spontaneous Hypoglycemia: The Role of Diet in Etiology and Treatment, *South. M. J.* **24**:249, 1931. John, H. J.: A Case of Hyperinsulinism Treated with Insulin: Preliminary Report, *Endocrinology* **17**:583, 1933. Conn, J. W.: The Advantage of a High Protein Diet in the Treatment of Spontaneous Hypoglycemia, *J. Clin. Investigation* **15**:673, 1936.

marked hypersensitivity to the normal stimulus for increasing the rate of combustion of carbohydrate, whether or not a rise of the blood sugar is the actual stimulus. Since a rise of the blood sugar results also from the administration of epinephrine, we considered it important to study in patients with hyperinsulinism the effect on the combustion of carbohydrate of hyperglycemia produced in this way. We are not aware of any similar metabolic study of this condition. (For a clinical description of the patient studied see our preceding report.⁵)

In the third place, the clinical observation that injections of a solution of epinephrine hydrochloride are frequently capable of controlling hypoglycemic attacks in cases of organic hyperinsulinism receives a clear explanation from the results of the present study. They justify a clinical procedure which seems indicated under certain circumstances.

METHOD

A respiration chamber⁸ designed for human subjects, with which data from long periods of continuous indirect calorimetry could be gathered, was used. The technic was the same as that described in the preceding paper.⁵ In addition, the subjects were taught to give themselves a subcutaneous injection of a solution of epinephrine hydrochloride at a given signal. The dose and the technic of administration were checked by observation through a sealed window of the chamber. Methods of analysis of blood, urine and gases were identical with those previously described.⁵ Constant diets were used in preparation for and during all experiments. Normal subjects under identical conditions were used as controls.

RESULTS

The table shows the results obtained from four hour periods of continuous indirect calorimetry. The results after the subcutaneous administration of a dose equivalent to 1 mg. of epinephrine hydrochloride are compared with those previously obtained in the postabsorptive state, the conditions of the experiments being otherwise identical. It is seen that this amount of epinephrine exerts no significant effects on the rate of combustion of carbohydrate. If influenced at all, the respiratory quotients are slightly decreased. Yet, as will be seen in figure 1, epinephrine provoked a marked increase of the blood sugar level both in the patient and in the control subjects. It should be recalled that under the same conditions of dietary preparation, the ingestion of 60 Gm. of dextrose resulted in a marked increase in the rate of combustion of carbohydrate by the controls and in an excessive increase by the patient.⁵

7. Footnote deleted by the authors.

8. Newburgh, L. H.; Johnston, M. W.; Wiley, F. H.; Sheldon, J. M., and Murrill, W. A.: A Respiration Chamber for Use with Human Subjects, *J. Nutrition* **13**:193, 1937.

Combustion of Carbohydrate, Fat and Protein During Four Hour Test Periods in Respiration Chamber

Subject	Preparatory Diet (5 Days), with Maintenance Calories		Test Dose in Chamber; Epinephrine hydrochloride, Mg.	Total Respiratory Quotient	Non-protein Respiratory Quotient	Total Heat Produced, Calories	Heat Produced, Protein Calories	Heat Produced, Non-protein Calories	Source of Nonprotein Calories, Percentage		Comment
	Carbo-hydrate, Gm.	Protein, Gm.							Carbo-hydrate	Fat	
Patient *.....	100	80	0	0.780	0.776	253	39	214	21.9	75.1	Before operation
Patient *.....	100	80	0	0.794	0.792	257	41	216	30.6	69.4	Before operation
Control *.....	100	80	0	0.782	0.778	328	56	272	25.6	74.4	
Control *.....	100	80	0	0.792	0.790	336	48	288	29.9	70.1	
Control *.....	100	80	0	0.791	0.790	335	48	287	29.9	70.1	
Patient.....	100	80	1	0.781	0.777	279	39	240	25.3	74.7	Before operation
Control.....	100	80	1	0.784	0.780	367	56	311	26.3	73.7	
Control.....	100	80	1	0.782	0.778	402	61	338	25.6	74.4	
Control.....	100	80	1	0.771	0.766	372	58	320	21.1	78.6	
Control.....	100	80	1	0.775	0.771	385	39	346	23.2	76.8	

* These data are those shown for experiment 3 in the table of our preceding paper.⁵ They are reproduced here for direct comparison with data obtained after the administration of epinephrine hydrochloride.

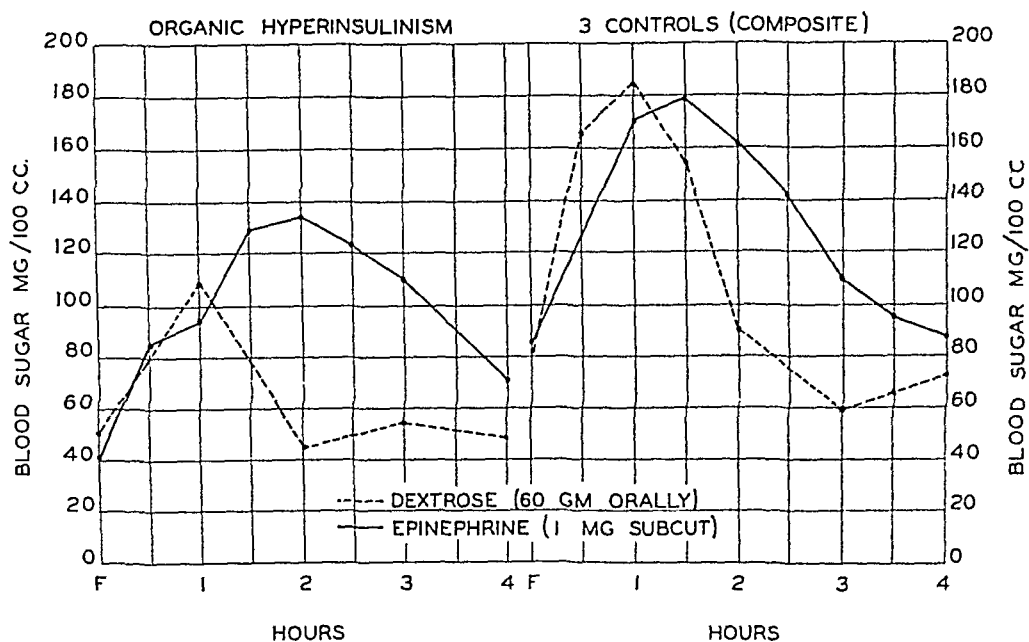


Fig. 1.—Comparison of glycemic responses of a patient with organic hyperinsulinism and of 3 normal subjects after the administration of epinephrine hydrochloride and after the administration of dextrose (preparatory diet: carbohydrate 100 Gm., protein 80 Gm. and maintenance calories).

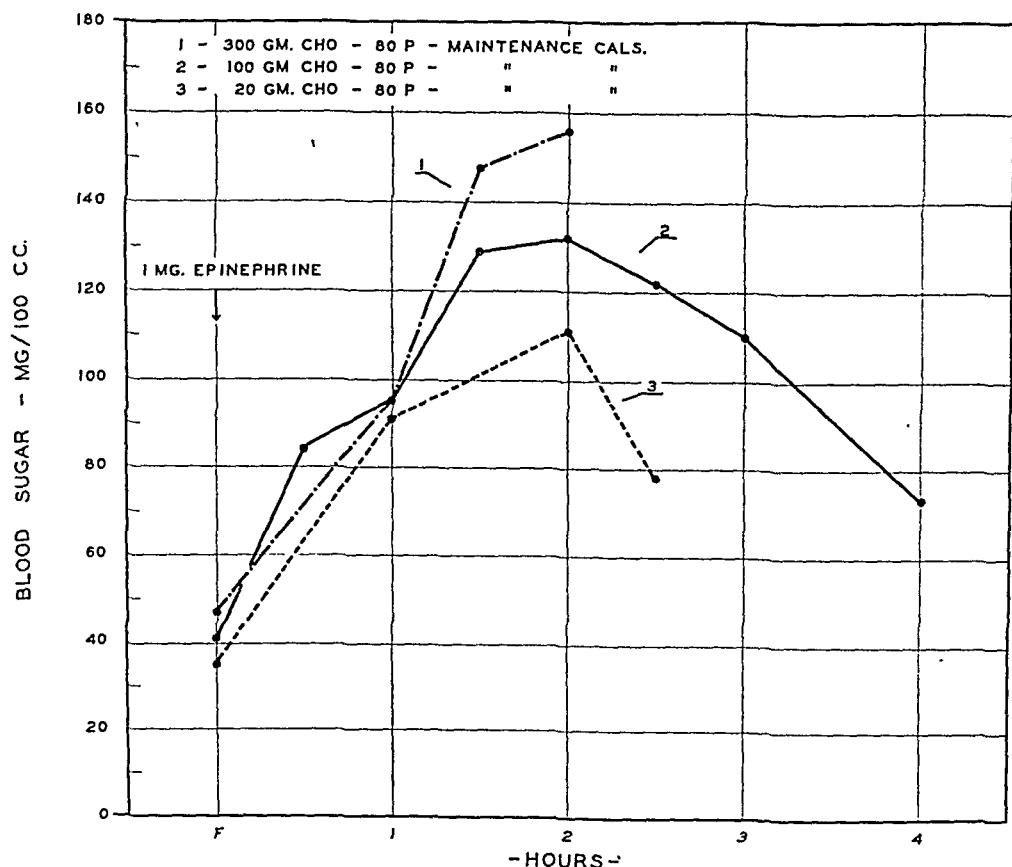


Fig. 2.—Effect of previous diet on glycemic responses to epinephrine hydrochloride.

Figure 1 compares the blood sugar curves of the patient and those of 3 control subjects after (1) the subcutaneous injection of epinephrine hydrochloride and (2) the ingestion of 60 Gm. of dextrose. In all cases the hyperglycemia produced by epinephrine was of the same magnitude as but was more prolonged than that observed after the ingestion of dextrose.

Figure 2 indicates that the glycemic response in the fasting state of a patient in organic hyperinsulinism to 1 mg. of epinephrine hydro-

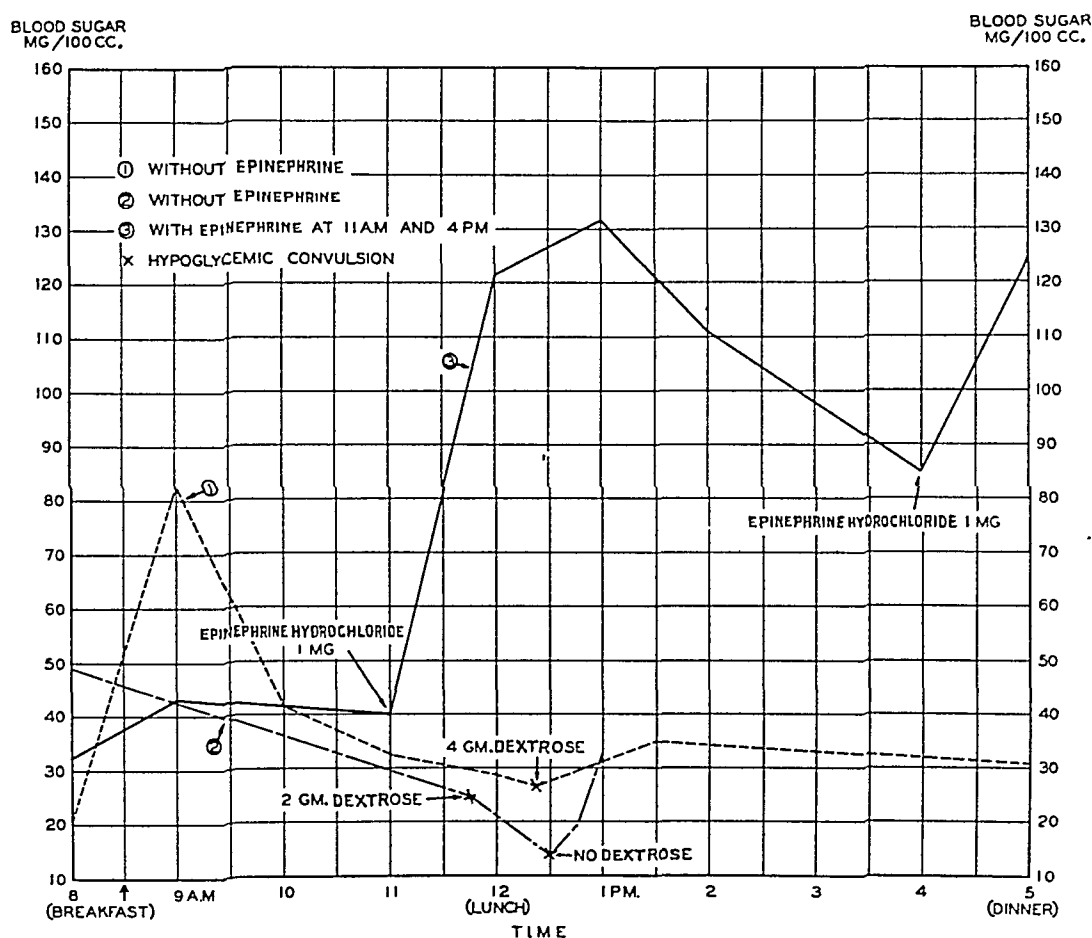


Fig. 3.—Effect of epinephrine hydrochloride on daily sugar curves (diet: carbohydrate 20 Gm., protein 50 Gm. and fat 137 Gm.).

chloride given subcutaneously is related to the carbohydrate content of the antecedent diet.

Results of a third experiment indicated the effectiveness of epinephrine hydrochloride in controlling hypoglycemic convulsions, even under conditions of carbohydrate privation. During an eleven day control period the patient was kept in bed and fed a diet which, although it provided enough calories for maintenance, contained only 20 Gm. of carbohydrate and 50 Gm. of protein for each twenty-four hours. Two to four hypoglycemic convulsions were observed daily. They occurred regularly at two times of day, namely, between 11:30 a. m. and 12:40 p. m. and

between 4:00 and 5:30 p. m. The blood sugar level during attacks ranged from 14 to 34 mg. per hundred cubic centimeters. For the next five days 1 mg. of epinephrine hydrochloride was given subcutaneously at 11:00 a. m. and at 4:00 p. m., the diet remaining the same. No attack occurred during this period. Figure 3 shows the blood sugar level on two successive days during the control period and the effect of epinephrine on the blood sugar level in the second period.

We performed a similar experiment, using 50 mg. of ephedrine sulfate orally six times daily in place of epinephrine hydrochloride. This substitute was only mildly effective. Hypoglycemic convulsions were delayed until from 2:00 to 3:00 p. m. but were not prevented.

COMMENT

The results indicate that the administration of epinephrine, in amount sufficient to produce a prolonged elevation of the blood sugar level, does not stimulate any increase in the rate of combustion of carbohydrate over that observed in the fasting state, either in persons with organic hyperinsulinism or in normal subjects. Previous observations^{1k} and the present ones suggest, on the contrary, that if the rate of oxidation of carbohydrate is at all affected by the amount of epinephrine administered, it is mildly depressed.⁹ It can be said, further, that, within the limits of these experiments the height per se of the blood sugar is not related to the rate of combustion of carbohydrate in persons with organic hyperinsulinism or in normal subjects.

We⁵ showed that the ingestion of dextrose results in a greatly accelerated rate of combustion of carbohydrate in normal subjects and in an abnormally great increase of the rate in a patient with organic hyperinsulinism. Comparable hyperglycemia (fig. 1) produced, on the one hand, by ingestion of dextrose and, on the other, by the administration of epinephrine hydrochloride produces entirely different effects on the combustion of carbohydrate. Otherwise stated, the addition to the body of extra carbohydrate from outside sources produces an acceleration of the rate of combustion of carbohydrate, while hyperglycemia of endogenous origin does not.

The fact that a rise in the level of the blood sugar induced by epinephrine does not produce a simultaneous increase in the rate of combustion of sugar becomes of practical importance in the medical management of persons with severe organic hyperinsulinism. It is agreed by all

9. Experiments such as these, in which the total respiratory gaseous exchange of a prolonged period is accounted for, eliminate the inaccuracies (produced by temporary shifts in acid-base balance after administration of epinephrine) which have been observed in "short run" collections of respiratory gases.

familiar with the problem that when certain clinical diagnostic criteria¹⁰ have been satisfied, an exploratory operation in search of an islet cell tumor of the pancreas should be done. Unfortunately, tumors are not always found, and the severe hypoglycemia must be treated medically. A diet low in carbohydrate is unsuccessful under these particular circumstances because the liberation of insulin cannot be sufficiently depressed by this means.⁵ One is consequently forced to give frequent feedings high in carbohydrate in an attempt to maintain the blood sugar above the "attack level." As was indicated, combustion of carbohydrate is tremendously stimulated under these conditions, and periodic convulsions result. In fact, continuous infusion of dextrose has been necessary in some cases in order to prevent hypoglycemia. The following facts make epinephrine a useful adjunct in the medical management of this condition: 1. The liver in cases of organic hyperinsulinism usually contains large amounts of glycogen.¹¹ 2. Some of this store of carbohydrate can be mobilized and delivered into the blood by the daily administration of epinephrine without increasing the rate of carbohydrate combustion. These experimental observations were put to clinical test (fig. 3). The use of 1 mg. of epinephrine hydrochloride twice daily was successful in preventing hypoglycemic convulsions on the same dietary plan which had resulted in two to four seizures daily. Wilder,^{11a} from his clinical observations, has made the suggestion that the use of epinephrine base in oil might be of benefit in this condition. As already stated, large doses of ephedrine sulfate were ineffective in controlling hypoglycemic attacks.

Finally, discrepancies in the glycemic response after administration of epinephrine hydrochloride in cases of organic hyperinsulinism can be related, at least in part, to differences in the antecedent diet of the patient. If all patients with organic hyperinsulinism were given equal opportunity to accumulate a glycogen reserve by means of a standard preparatory diet,¹² the use of a test dose of epinephrine hydrochloride might bring out significant differences in types and degrees of this disease.

CONCLUSIONS

1. Epinephrine hydrochloride in sufficient amount to produce prolonged hyperglycemia does not increase the postabsorptive rate of com-

10. Conn, J. W.: The Spontaneous Hypoglycemias: Importance of Etiology in Determining Treatment, *J. A. M. A.* **115**:1669 (Nov. 16) 1940.

11. (a) Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*, Philadelphia, W. B. Saunders Company, 1940, p. 376. (b) Warren, S.: *Pathology of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1938, p. 192. (c) Conn and Conn.⁵

12. Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, *Am. J. M. Sc.* **199**:555, 1940.

bustion of carbohydrate, either in persons with organic hyperinsulinism or in normal persons. The respiratory quotient, if at all affected, is slightly depressed.

2. The average height per se of the blood sugar does not control the rate of combustion of carbohydrate. Hyperglycemia of comparable magnitude, produced, on the one hand, by administration of epinephrine hydrochloride and, on the other, by ingestion of dextrose, is associated with wide differences in the rate of oxidation of carbohydrate.

3. In organic hyperinsulinism a rise in blood sugar associated with absorption of dextrose is accompanied by tremendously excessive combustion of carbohydrate. Hyperglycemia produced by epinephrine hydrochloride alone results in no greater oxidation of sugar than that observed in the postabsorptive state.

4. When medical management of patients with severe organic hyperinsulinism becomes necessary, the daily administration of epinephrine hydrochloride is a useful adjunct because (1) the hyperglycemia thus produced is not accompanied by increased combustion of sugar and (2) the excessive inhibition of hepatic glycogenolysis due to hyperinsulinism is partially released.

5. Differences in the glycemic response to epinephrine in cases of organic hyperinsulinism may be due, in part, to the lack of standardized dietary preparation for the test.

METABOLISM IN ORGANIC HYPERINSULINISM

III. EFFECTS OF ADRENAL CORTICAL EXTRACT ON BLOOD SUGAR AND ON SODIUM AND NITROGEN EQUILIBRIUM

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In 1932 Britton and Silvette¹ demonstrated that the secretion of the adrenal cortex is involved in the metabolism of carbohydrate. The experiments of Long and Lukens in 1936,² indicating that severe pancreatic diabetes could be greatly ameliorated by bilateral adrenalectomy, stimulated further investigation of the role of the adrenal cortex in carbohydrate metabolism. Much information has since been obtained with respect to the physiologic processes involved and the specific fractions of the adrenal cortical secretion responsible for the effects produced.³

Since 1937 evidence has been presented which indicates that adrenal cortical extracts are capable of raising the blood sugar of normal, starving, starving-hypophysectomized, partially depancreatized and depancreatized-adrenalectomized animals.⁴ Further, it has been reported⁵ that normal mice are rendered resistant to the hypoglycemic

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The expense of these studies was defrayed in part by a grant from the Horace H. Rackham and Mary A. Rackham Foundation.

1. Britton, S. W., and Silvette, H.: Effects of Cortico-Adrenal Extract on Carbohydrate Metabolism in Normal Animals, *Am. J. Physiol.* **100**:693, 1932.

2. Long, C. N. H., and Lukens, F. D. W.: Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in Cats, *J. Exper. Med.* **63**:465, 1936.

3. Long, C. N. H.: Diabetes Mellitus in the Light of Our Present Knowledge of Metabolism, *Tr. & Studies Coll. Physicians Philadelphia* **7**:21, 1937.

4. (a) Corey, E. L., and Britton, S. W.: Hypophyseal and Adrenal Interrelationships and Carbohydrate Metabolism, *Am. J. Physiol.* **126**:148, 1939. (b) Long, C. N. H., and Katzin, B.: Effect of Adrenal Cortical Hormone on Carbohydrate Stores of Fasted Hypophysectomized Rats, *Proc. Soc. Exper. Biol. & Med.* **38**:516, 1938. (c) Corey, E. L.: Hypophyso-Adrenal Synergy and Carbohydrate Metabolism, *Am. J. Physiol.* **126**:470, 1939. (d) Fry, E. G.; Long, C. N. H., and Ritter, H. B.: The Aggravation of Pancreatic Diabetes of Adrenal Cortical Extract, *ibid.* **126**:497, 1939. Long.³

5. Jensen, H., and Grattan, J. F.: The Identity of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, *Am. J. Physiol.* **128**:270, 1940.

effects of insulin by the previous administration of adrenal cortical extracts. These observations, indicating an "anti-insulin" effect of such substances, suggested this investigation. It was felt that cases of organic hyperinsulinism in human beings afforded an opportunity to test the practicability of the laboratory findings.

The subject of this study was a 60 year old woman who was suffering from severe spontaneous hypoglycemia and who, subsequently, was completely cured by the surgical removal of four islet cell adenomas.⁶ In order to demonstrate physiologic activity of the adrenal cortical extract used, sodium and nitrogen balance studies were conducted along with the observations on the blood sugar levels.

METHODS

For the entire period of study the patient was confined to bed, except for the collection of urine and feces, which was facilitated by the use of a commode beside the bed. The carefully weighed diet, which provided enough calories for maintenance, was constant from day to day. The sodium and the nitrogen content of the diet was determined by analysis. The fluid intake was constant. Ten grams of sodium chloride per day, in tablet form, was given with meals.

Determinations of blood sugar were done by the Benedict method.⁷ Food and urinary sodium were determined according to the method of Butler and Tuthill,⁸ and food, urinary and fecal nitrogen, by the Kjeldahl method.

Adrenal cortical extract⁹ was used throughout. The sodium and nitrogen content of the extract was determined and was found to be negligible.

RESULTS

The results are graphically summarized in figure 1.¹⁰

Blood Sugar.—A diet low in carbohydrate (carbohydrate 20 Gm., protein 50 Gm. and fat 137 Gm.) was used in order to provoke frequent hypoglycemic attacks, the frequency of which could be compared with and without the daily intramuscular injection of 30 cc. of adrenal cortical

6. Conn, J. W., and Conn, E. S.: Metabolism in Organic Hyperinsulinism: I. Quantitative Studies of the Utilization of Carbohydrate Under Various Conditions, J. Clin. Investigation, to be published.

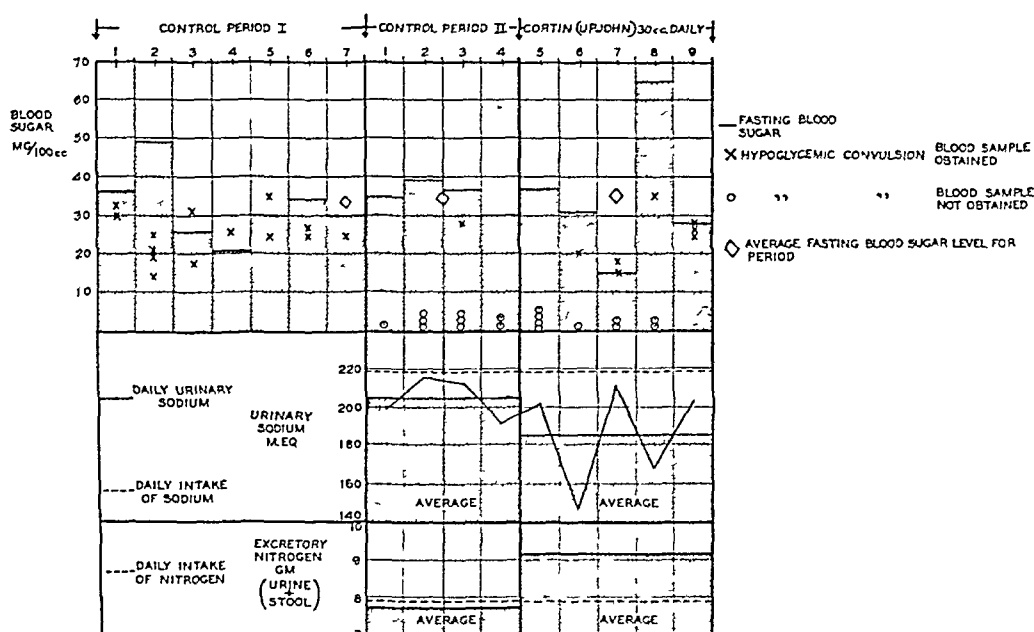
7. Benedict, S. R.: The Analysis of Whole Blood: II. The Determination of Sugar and of Saccharoids (Non-Fermentable Reducing Substances), J. Biol. Chem. **92**:141, 1931.

8. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**: 171, 1931.

9. The extract used (cortin-Upjohn) was supplied by Dr. E. Gifford Upjohn and the Upjohn Co.

10. Control period II was preceded by three days of the control regimen to allow the patient to come into equilibrium with her diet. Determinations were begun on the fourth day. The first day of control period II, therefore, is the fourth day of the control regimen.

extract (5 cc. in each buttock three times daily). The level of fasting blood sugar was determined daily, and the level of the blood sugar during convulsions was obtained in the majority of attacks. Note in the two separate control periods that the average values for the fasting blood sugar were 33 and 35 mg. per hundred cubic centimeters, respectively. During the period of administration of adrenal cortical extract there was somewhat greater variation, both the highest and the lowest values having been obtained then. The average value for the period, however, was 35 mg. per hundred cubic centimeters. Convulsive attacks, occurring between levels of 14 and 35 mg. per hundred cubic centimeters, came one to four times a day, with an average of two times per day in the control periods. When adrenal cortical extract was given they occurred



Effect of adrenal cortical extract on the blood sugar level and on the sodium and nitrogen balance in a case of organic hyperinsulinism (constant diet: carbohydrate 20 Gm., protein 50 Gm., fat 137 Gm. and sodium chloride 10 Gm.).

two to four times daily, averaging three times per day. Thus, the amount and kind of adrenal cortical extract used resulted in no apparent "anti-insulin" or blood sugar-raising effect in this case of organic hyperinsulinism.

Sodium Balance.—It may be seen that during the period of administration of the extract there occurred an average daily retention of 22 milliequivalents of sodium, as compared with the quantities excreted during the control period. This represents a retention of 10 per cent of the daily total intake of sodium. It should be noted that wide daily swings of retention and "rebound," above and below the average value, occurred during the period when adrenal cortical extract was given.

This phenomenon has been described by Thorn¹¹ as occurring in normal human beings receiving large amounts of adrenal cortical extract.

Nitrogen Balance.—Nitrogen equilibrium was maintained during the control period. The injection of 30 cc. of adrenal cortical extract daily resulted in an average daily increase of 1.5 Gm. of excretory nitrogen. This amounted to a 20 per cent increase in the excretion of nitrogen over excretion during the control period. The occurrence of a similar increase in nitrogen excretion of rats receiving large doses of adrenal cortical extract has been demonstrated by Long, Katzin and Fry.¹²

COMMENT

That adrenal cortical extracts are capable of raising the blood sugar level and of increasing the content of glycogen in the liver and muscles of animals kept under a variety of conditions has been indisputably established.¹³ It has been shown further that certain fractions of adrenal cortical extracts are much more active than others in these respects.¹² Jensen and Grattan⁵ expressed the belief that the so-called glycotropic (anti-insulin) factor of anterior pituitary extracts is identical with the adrenotropic factor and that the anti-insulin effect is produced by virtue of stimulation of the adrenal cortex. They were able to prevent insulin convulsions in mice by previous administration of anterior pituitary extracts containing the adrenotropic fraction, adrenal cortical extracts and corticosterone acetate. Other fractions of anterior pituitary extract (free from the adrenotropic factor) were ineffective.

It must be realized that in all of the aforementioned experiments the amounts of material required to produce these effects in animals have been enormous. It is easily calculated from the experiments of Jensen and Grattan⁵ that it required in the mouse 12.5 mg. of crystalline corticosterone acetate (one of the fractions presumably concerned in the metabolism of carbohydrate) to counteract the hypoglycemic effect of 1 unit of insulin¹⁴ and that it required 1,000 dog units of Swingle's adrenal cortical extract to do the same thing. Long,³ employing the same preparation as that used in this study, gave 48 cc. per kilogram of body weight to produce a substantial rise in blood sugar and liver glycogen and an increased excretion of nitrogen in rats. These amounts are, of

11. Thorn, G. W.: Effect of Cortical Hormone on Renal Excretion of Electrolytes in Normal Subjects, *Proc. Soc. Exper. Biol. & Med.* **36**:361, 1937.

12. Long, C. N. H.; Katzin, B., and Fry, E. G.: Adrenal Cortex and Carbohydrate Metabolism, *Endocrinology* **26**:309, 1940.

13. Britton and Silvette.¹ Long.³ Footnotes 4 *a*, *b* and *c*.

14. Kuizenga and Cortland (Fractionation Studies on Adrenal Cortex Extract with Notes on the Distribution of Biological Activity Among the Crystalline and Amorphous Fractions, *Endocrinology* **24**:526, 1939) were able to obtain a yield of only 68 mg. of crystalline corticosterone acetate from 880 Kg. of beef adrenal gland.

course, of an entirely different order of magnitude from what has ever been given a human being, even when allowance is made for differences in metabolic rate and in species. It is not surprising, therefore, that the daily administration to our patient of 30 cc. of adrenal cortical extract (three to four times the amount required to control severe Addison's disease) was incapable of raising the level of blood sugar or of exerting any apparent anti-insulin effect.

On the other hand, a definite physiologic effect on the metabolism of sodium and of nitrogen was observed. This amounted to a daily retention of 10 per cent of the ingested sodium and an excretion of nitrogen which was 20 per cent in excess of the daily intake. The increased catabolism of protein induced by adrenal cortical extract indicates an excessive destruction of body protein, which amounts to about 9.4 Gm. daily. No more than 5 Gm. of dextrose for each twenty-four hour period would be derived in this process. Long³ expressed the opinion that the source of the extra carbohydrate observed in animals treated with adrenal cortical extracts is found in the increased destruction of protein. Even in the absence of increased utilization of sugar one would hardly expect the addition of 5 Gm. of dextrose poured into the blood evenly over a twenty-four hour period to have any significant effect in raising the blood sugar of an adult human subject.¹⁵ It would appear, therefore, that the rise of blood sugar and glycogen content, demonstrated in laboratory animals, is the result of the use of massive doses of adrenal cortical extracts and their purified derivatives. Physiologic activity of adrenal cortical extracts with regard to sodium and nitrogen metabolism is demonstrable in human beings with much smaller doses.

CONCLUSIONS

In a proved case of organic hyperinsulinism the daily administration of 30 cc. of adrenal cortical extract exerted no apparent anti-insulin or blood sugar-raising effect.

Simultaneous sodium and nitrogen balance studies indicated the potency of the extract used. There occurred a retention of 10 per cent of the ingested sodium and an excretion of nitrogen which was 20 per cent in excess of the intake.

The amounts of adrenal cortical materials used to produce a rise of the blood sugar in laboratory animals are relatively so large that (1) the results may represent a response which is possible only under distinctly abnormal circumstances and (2) clinical use of the material as an insulin antagonist is impractical with the adrenal cortical extracts now available.

15. Conn, J. W., and Newburgh, L. H.: The Glycemic Response to Isoglucogenic Quantities of Protein and Carbohydrate, *J. Clin. Investigation* **15**:665, 1936.

HYPOTHERMIA

REPORT OF A CASE IN WHICH THE PATIENT DIED DURING THERAPEUTIC
REDUCTION OF BODY TEMPERATURE, WITH METABOLIC
AND PATHOLOGIC STUDIES

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A substantial reduction of body temperature has been employed by several investigators in recent years as a useful therapeutic procedure. It was devised by Smith and Fay¹ originally for the treatment of patients with metastatic malignant growths and has been extended subsequently to the treatment of patients with other conditions.² The depression in the internal body temperature which may be produced by the general application of cold to the subject's skin belies common opinion concerning the minimum critical temperature. Internal body temperatures which range from 80 to 90 F. may be maintained continuously, if due precautions are exercised, for as long as seven days. After such a treatment the patient appears to have suffered no undesirable effects. Smith and Fay chose hibernation as a fitting term for the treatment, while others have called it refrigeration, freezing, frozen sleep and crymotherapy. It is believed that a valid criticism may be offered against the selection of any of them. Hypothermia,² on the other hand, is exempt from such criticisms and is thought to be a most appropriate term. It will be used to connote a general lowering of the internal temperature of the body to the point where freezing supervenes.

When a new and radical procedure, as in this instance, is introduced into medical therapeutics, as complete data as possible concerning the

This study was aided by grants from the Lucius N. Littauer Foundation and the Corn Industries Research Foundation.

From the McLean Hospital, Belmont, Mass.; the Medical Clinic of the Massachusetts General Hospital, and the Fatigue Laboratory, Harvard University.

1. Smith, L. W., and Fay, T.: Observations on Human Beings with Cancer, Maintained at Reduced Temperatures of 75°-90° Fahrenheit, *Am. J. Clin. Path.* **10:1**, 1940.

2. Talbott, J. H.: The Physiologic and Therapeutic Effects of Hypothermia, *New England J. Med.* **224:281**, 1941.

direct, as well as the indirect, effects should be collected. The minimum requirements for a comprehensive study might well embrace therapeutic results, physiologic and biochemical variations and morphologic changes. An attempt has been under way recently to fulfil these requirements, and toward this end certain studies of hypothermia either have been reported³ from our laboratory or are in preparation. This communication presents additional data on the physiologic changes observed during hypothermia, but it is concerned particularly with 1 patient in our series who died during a hypothermic treatment. The patient was a 46 year old man suffering from schizophrenia, who died after two days of continuous hypothermia, while the body temperature was returning to normal.

Reports in the literature of patients who have died after accidental exposure to cold or who have suffered from an advanced stage of a metastatic malignant growth and have died during hypothermia have been inadequate in one respect. In neither circumstance could one be certain that the observed changes were associated with hypothermia per se. On the other hand, the patient under discussion was physically sound before the treatment and was suffering from a mental disorder only. No portion of the body was frozen during treatment, and the observed morphologic changes are believed to be intimately associated with a reduction of body temperature and not complicated by other factors or processes.

The procedure for the induction of hypothermia has been described⁴ and will not be repeated in detail. It involves essentially the exposure of an anesthetized nude subject to a cold environment. Cracked ice or blankets especially constructed for the circulation of a refrigerant suffice. In our studies hypothermia was achieved by the latter means. Shortly after exposure to such an environment, the heat-regulatory mechanism is overpowered, and a steady decline in body temperature follows. During hypothermia, the temperature level of the body may be maintained by the regulation of the environmental temperature.

REPORT OF CASE

W. D., a white, American-born man aged 46, suffered from symptoms of mental disease for more than ten years. He was admitted first to McLean Hospital in 1931. He spent the greater part of the following nine years in that hospital. A diagnosis of schizophrenia was made in 1934. An extremely poor prognosis regarding his mental disease was expressed by several psychiatrists at that time

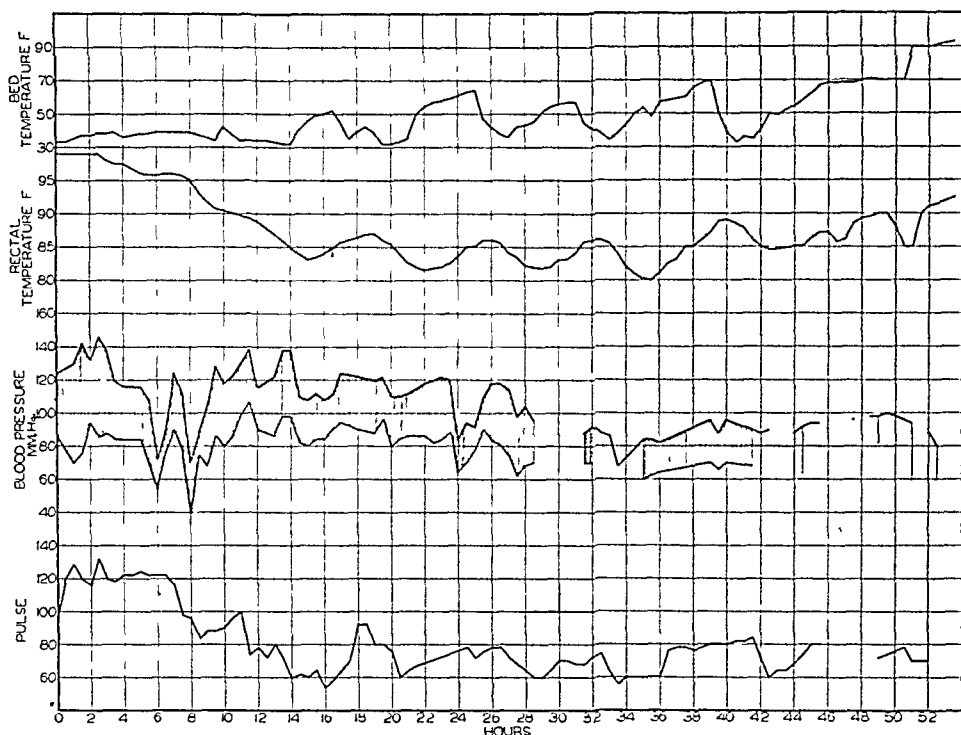
3. (a) Talbott, J. H., and Tillotson, K. J.: The Effects of Cold on Mental Disorders: A Study of Ten Patients Suffering from Schizophrenia, *Dis. Nerv. Syst.* **2**:116, 1941. (b) Dill, D. B., and Forbes, W. H.: Respiratory and Metabolic Effects of Hypothermia, *Am. J. Physiol.* **132**:685, 1941. (c) Talbott.²

4. Smith and Fay.¹ Talbott.²

and was confirmed by others after that. He was given several shock treatments with insulin in 1938. His mental condition became decidedly worse after these.

His physical condition had been satisfactory at all times. A periodic physical examination, as well as the examination which preceded the induction of hypothermia, revealed nothing abnormal. His blood pressure was 124 systolic and 88 diastolic; his body weight was 162 pounds (73.5 Kg.). Frequent routine examinations of the urine and the blood had yielded normal results. Because of these findings, together with the unsatisfactory mental state, it was decided to treat him with a reduction of body temperature.

Hypothermia was instituted on June 19, 1940. Twenty minutes before the induction he was given 0.24 mg. of pentobarbital sodium intramuscularly, followed in eighteen minutes by 0.8 Gm. of evipal sodium (the sodium salt of n-methyl-C-C-



Record of fluctuation in bed temperature and the rectal temperature, blood pressure and pulse rate of a schizophrenic patient during induced hypothermia.

cyclohexylmethyl barbituric acid) administered intravenously. During the first seven hours of hypothermia he was given 1.3 Gm. additional of the last-named drug in divided doses. No other sedative, anesthetic or medicament was administered until he went into circulatory collapse shortly before death two days later.

Eleven hours after induction of hypothermia a nasal gavage tube was inserted. Fifty cubic centimeters of a 5 per cent solution of dextrose in a physiologic solution of sodium chloride was instilled through the tube every hour thereafter. Various investigational procedures were carried out from time to time and were not upsetting to the patient. These included metabolic measurements; electrocardiographic, electroencephalographic and teleroentgenographic examinations of the heart and lungs; drawing of blood for analysis, and determination of circulation time and of renal clearance.

The body temperature reached 83.5 F. sixteen hours after the beginning of the induction. As indicated in the chart, it remained below 98 F. for fifty hours and below 95 F. for forty-five hours before reaching a minimum of 80 F. The initial fall in temperature was slightly slower than the average in our experience, but this patient had a large frame and the room temperature was high. These are adequate reasons for a slow reduction in body temperature.

The clinical response during the first two days under treatment was similar to that observed in other patients, and nothing was noted which gave rise to any undue alarm. During the first three hours of induction the blood pressure and pulse rate were strong and of good quality. A drop in blood pressure followed, but this is the usual response, and it was not considered to be disturbing. Shivering was apparent intermittently throughout the treatment. Below 95 F. there appeared to be no correlation between the severity of shivering and further reduction in body temperature. The duration of the shivering spells was as long when the temperature was below 85 F. as it was at other temperatures.

After the treatment had continued for approximately two days it was decided arbitrarily to terminate it. The flow of refrigerant through the coils in the blankets was stopped. The body temperature rose slowly to 90 F. Nothing had developed up to this time to give rise to serious apprehension for the physical condition of the patient. Owing to a mistake in orders, the patient was taken out of the blankets at this point and allowed to drink water and hot bouillon. A drop of 5 F. in body temperature followed shortly thereafter, which was thought to be incorrect and attributed to a poorly inserted rectal thermocouple. It is believed now that the thermocouple was properly inserted and that the temperature drop as recorded was correct. The blood pressure was 94 systolic and 60 diastolic. The patient was then replaced between the temperature-controlled blankets, and instead of a cold solution circulating through the blankets, as we now know should have been ordered, a solution above body temperature was employed. The body temperature fluctuated rather rapidly, but before the full significance of this was appreciated, the patient was in profound circulatory collapse. The color was cyanotic, the respirations were gasping and shallow and the peripheral pulse was not obtainable. An unsuccessful attempt was made to administer intravenously a solution of dextrose and sodium chloride. Oxygen inhalation and injections of caffeine with sodium benzoate and ephedrine hydrochloride were given terminally, without demonstrable effect. The rectal temperature was 92.5 F. when the patient was pronounced dead, less than one hour after the onset of circulatory shock. This was the maximum it had reached for more than two days. A complete autopsy was performed four hours later.

Laboratory Studies.—Routine examinations of the urine were negative for dextrose, albumin and formed elements, but all were positive for acetone and diacetic acid.

Results of roentgenographic examination of the chest were reported by Dr. J. R. Lingley as follows:

"The transverse measurements of the heart shadow and chest taken at 7 feet (2.1 meters) with a fifteen second exposure are:

Duration of Treatment, Hr.	Heart, Cm.	Chest, Cm.	Rectal Temperature, F.
0.....	12.7	27.1	98
24.....	12.4	26.8	83
34.....	11.5	27.2	82
48.....	12.3	27.5	89

"Detail in the lung is obscured by motion, and interpretation of the pathologic condition of the lung is impossible."

The concentrations of the constituents of the blood are given in table 1. The methods for analysis of the blood constituents have been described previously.⁵

The electrocardiograms were interpreted by Dr. Ashton Graybiel as follows:

Before hypothermia: "The rhythm is normal, and the rate is 90 beats per minute. The P waves are normal. The PR interval measures 0.18 second. The QRS complexes are slightly slurred, but their duration is 0.08 second, which is within normal limits. The QRS voltage is low but within the normal range. The ST segments are slightly elevated in leads I and II. The T waves are tall and upright in all leads."

After twenty-four hours of hypothermia: "The rhythm is normal, and the rate is 60 beats per minute. The P waves and the PR interval remain unchanged. There has been a slight increase in the amplitude of the R waves. The ST segments are displaced upward to a slightly greater extent in leads I and II than in the control record."

After thirty-four hours of hypothermia: "The rhythm is normal, and the rate is 55 beats per minute. Because of somatic tremor the P waves cannot be delineated with sufficient accuracy to determine the PR interval. The QRS complexes appear to be somewhat longer in duration, but the measurements are not accurate. It is possible that some slight degree of intraventricular block is present. The upward displacement of the ST segments in leads I and II is increased further and is definitely abnormal. The T waves are low in amplitude in leads I and II and are isoelectric in lead III."

After forty-eight hours of hypothermia: "The rhythm is normal, and the rate is 57 beats per minute. The P waves are normal. The PR interval is 0.18 second. The QRS complexes are similar to those in the control record. The ST takeoff is abnormally high in leads I and II. This segment shows considerable concavity in all three leads. The T waves are slightly lower than in the first record."

Postmortem Examination.—Because of the interest in this case a complete and extensive autopsy was performed. Only the significant findings will be enumerated. Chemical analyses were made of several different organs and tissues of the body (table 2) in addition to the morphologic studies.

Except for moderate rigor mortis and marked lividity, the exterior aspect of the body was not remarkable.

The brain weighed 1,450 Gm. and was grossly normal. Microscopically there were a few foci of probable degeneration in the cortical nerve cells. A few fresh subependymal hemorrhages were visible in the wall of the third ventricle; there was no cellular reaction. The pituitary was enlarged, measuring 1.9 by 1.2 by 0.8 cm. On section, it had a brownish gray mottled appearance, with a soft hemorrhagic circumscribed area 0.6 cm. in diameter. Microscopic examination of this area showed it to be a small chromophobic adenoma.

Several small foci of terminal bronchopneumonia were scattered through the lower lobes of both lungs, more marked in the right. This observation was verified

5. Talbott, J. H.: Interpretations of Clinical Chemical Procedures, Ohio State M. J. **35**:137, 1939. Dill and Forbes.^{3b}

TABLE 1.—*Experimental Observations on Blood*

Time, Hr.	Whole Blood				True Plasma, or Serum										Comment	
	Rectal Tem- pera- ture, F.	Oxygen Capac- ity, Volume Per Cent	Oxygen Satura- tion, Per Cent	Total Carbon Dioxide, Volume Per Cent	Total Base, mEq. per Liter	Sodium, mEq. per Liter	Potas- sium, mEq. per Liter	Cal- cium, mEq. per Liter	Chloride, mEq. per Liter	Phos- phate, Mg. per 100 Cc.	Protein, Gm. per 100 Cc.	Lactate, Mg. per 100 Cc.	Urate, Mg. per 100 Cc.	Non- protein Nitrogen, Mg. per 100 Cc.		
0	98	19.3	100.0	46.5	150.0	136.8	4.2	4.7	105.1	2.3	6.5	2.3	24	7.37	Arterial blood
7	96	21.1	98.8	38.0	147.5	136.5	4.4	...	101.5	...	7.2	19.1	10.2	..	7.31	Arterial blood
21	82	22.2	100.0	33.8	146.0	137.0	4.5	4.3	102.8	3.8	7.2	56.1	40	7.38	Arterial blood
35	80	150.5	137.8	5.4	6.1	7.1	10.5	55	Venous blood
45	86	23.3	93.8	17.5	148.5	136.3	4.0	3.8	100.0	5.0	6.2	23.0	12.6	60	7.22	Arterial blood
18	89	150.5	134.5	4.8	4.0	105.1	11.5	70	Venous blood

by microscopic examination, which revealed scattered alevoli filled with polymorphonuclear leukocytes and a few red cells.

The heart weighed 300 Gm. and was normal except for a small patent foramen ovale and slight atheromatous thickening of the aortic cusp of the mitral valve. Both coronary arteries showed moderate atheromatous changes, without appreciable narrowing of the lumens. Such changes also occurred in the aorta, with some calcification in the abdominal portion.

The kidneys weighed 200 Gm. and, except for slight arteriosclerotic changes consistent with the patient's age, were normal. There was slight hemorrhagic cystitis.

The thyroid, liver, spleen, pancreas and adrenal glands were normal, both grossly and microscopically.

The morphologic diagnoses included terminal bronchopneumonia, moderate sclerosis of the aorta and coronary arteries and slight renal arteriosclerosis, hemorrhagic cystitis and chromophobic adenoma of the pituitary gland.

TABLE 2.—*Chemical Constituents of Tissue*

Tissue	Water, Gm. per 100 Gm. of Tissue	Sodium, mEq. per Kg. of Water	Potassium, mEq. per Kg. of Water	Calcium, mEq. per Kg. of Water
Patient W. D.				
Psoas muscle.....	77	29	141	8
Heart.....	79	40	116	3
Liver.....	73	72	84	4
Kidney.....	79	72	79	5
Brain.....	78	77	166	8
Normal Subjects ²⁰				
Muscle.....	79	39	118	5
Heart.....	77	110	83	7
Liver.....	79	104	70	8
Kidney.....	80	90	56	13
Brain.....	90	83	94	7

COMMENT

The descriptions in the available literature of the morphologic changes associated with hypothermia fall into one of three classes: those concerned with (1) animals which have been exposed experimentally to cold and in which temperature in many instances has reached lower levels than are observed in human subjects; (2) human beings who have been exposed accidentally to the cold, as sometimes happens during alcoholic intoxication, and many of whom have had one or more extremities frozen, and (3) human subjects in whom hypothermia has been induced for the treatment of extensive or metastatic malignant growths. It is apparent that under none of these conditions can the effect of cold per se on previously healthy tissue be ascertained. The report of Smith⁶ is the closest approach that we

6. Smith, L. W.: Pathologic Changes Observed in Human Tissues Subjected to Subcritical Temperatures, *Arch. Path.* **30**:424 (July) 1940.

have discovered to the uncomplicated effect of cold on normal tissue. He has had opportunity in recent years to study the pathologic changes in 60 patients who have undergone one or more hypothermal treatments. He concluded that the action of cold, within the range studied, produced little morphologic alteration of normal tissue.

In this study we are concerned principally with the anatomic changes in the lungs, heart, kidneys and brain. Congestion of the lungs following exposure to cold has been observed in animals,⁷ as well as in human beings.⁸ Because of the prejudice that chilling predisposes to pneumonia it is important to evaluate as best we can this observation. None of the patients reported in the literature to have died after accidental exposure were thought to have had frank bronchopneumonia. Death was usually attributed to cardiac failure. During the past year we have supervised more than thirty hypothermal treatments. In all cases the patients were without clinical evidence of bronchopneumonia during or after the treatment and the roentgenograms of the chest were grossly normal also. The roentgen ray equipment permitted only a slow exposure, however, and fine pulmonary details were not evident. In none of the roentgenograms were large areas of consolidation visible.

Many patients with various types of cancer who were studied post mortem by Smith showed morphologic evidence of bronchopneumonia. He concluded, however, that in cases in which cancer was not a clinical terminal event the danger of fatal bronchopneumonia was negligible. In the case we report here the lungs showed patchy bronchopneumonia. It was the opinion of Dr. Benjamin Castleman, the pathologist, that it was not an overwhelming process and, other things being equal, was not extensive enough to cause death. At no time did our patient cough or raise bloody sputum.

The observed changes in the lungs were produced by at least two processes, i. e., slowing of the circulation and prolonged maintenance of the supine position. A slowing of the circulation is a secondary effect of peripheral vasoconstriction, expression of fluid from the vascular bed⁹ and parenchymatous edema. The venous congestion of the lungs and interstitial edema may be identical to that observed by Walther^{7a} in animals exposed to the cold. Impedance of gas exchange

7. (a) Walther, A.: Beiträge zur der Lehre von der thierischen Wärme, Virchows Arch. f. path. Anat. **25**:414, 1862. (b) Giese, E.: Experimentelle Untersuchung über Erfrierung, Inaug. Dissert., Jena, Berlin, L. Schumacher, 1901.

8. Nicolaysen, J.: Abrupt Fall in Body Temperature as the Result of Chilling, Norsk mag. f. lægevidensk. **5**:44, 1875. Smith.⁶

9. Benson, S.: Volume Changes in Organs Induced by the Local Application of External Heat and Cold and by Diathermy, Arch. Phys. Therapy **15**: 133, 1934.

across the alveolar membrane undoubtedly complicates the attempt of the organism to maintain homeostasis. Maintenance of the supine position during treatment is not ideal, but with the technic we employ at present it seems unavoidable. If cracked ice and a cold room, rather than especially constructed blankets, are available for induction, the position of the patient may be changed periodically and the untoward effect of hypostasis minimized.

It is concluded that while our patient had patchy areas of bronchopneumonia he did not die primarily because of them. Further evidence that fatal bronchopneumonia is not to be anticipated during or after hypothermia emanates from the observation that during periods of reduced temperatures practically complete bacteriostasis for ordinary pathogenic organisms exists.⁶ Similar findings were reported by Chodounský¹⁰ for animals. Two groups were exposed to virulent organisms. The control group was maintained at the usual environmental temperature and suffered a mortality of 63 per cent. The group that was chilled before exposure to the infectious agent, however, suffered a mortality of only 39 per cent.

A study of the morphologic changes in the heart is of great practical significance, since most patients who die after exposure suffer from terminal cardiac failure. The patient whose case is reported in this communication, as well as several studied by Smith, showed myocardial degeneration and atherosclerosis of the coronary vessels. It is to be doubted that hypothermia produces myocardial degeneration or coronary sclerosis. Hypothermia, however, imposes on the heart and blood vessels a severe burden, which they may be unable to withstand. This burden is produced by hemoconcentration, diminution in blood pressure and impaired oxygen transport.^{3b} A temporary additional burden may appear periodically during restoration of body temperature. As the temperature is allowed to rise, by virtue of an increase in environmental temperature, peripheral vasodilatation is inevitable. With a rapid and sudden expansion of the vascular bed, the heart becomes inefficient in its ability to supply blood to the heart and brain. Usually this can be controlled. At the time our patient was studied the full significance of keeping vascular changes under control was not appreciated. When the patient went into circulatory collapse, because of peripheral dilatation, additional heat was applied to the skin and the vasomotor response was aggravated. With our present understanding of the physiologic changes which accompany hypothermia, cold rather than heat should have been applied. It is apparent that the mechanism of vasomotor collapse occurring during restoration of body temperature

10. Chodounsky, K.: *Erkältung und Erkältungskrankheiten*, Vienna, J. Šafař, 1907.

in hypothermia is quite different from that of vasomotor collapse occurring in surgical or medical shock.

The observations on heart size by roentgen ray examination and on cardiac function by electrocardiographic study require little discussion. It is debatable whether the progressive diminution in heart size during treatment is significant, but one can state definitely that no increase in diameter was noted. The electrocardiogram taken before hypothermia was within normal limits. The most marked changes were observed in the tracing taken thirty-four hours after induction of hypothermia and included slowing of the heart rate, elevation of the ST segments in leads I and II and lowering of the amplitude of the T waves in all leads. These abnormalities had in large part disappeared by the time the last tracing was taken.

We do not intend to imply that the cardiovascular system is the only one seriously affected by hypothermia. A disintegration of its function has been emphasized, because ominous consequences develop rapidly under stress. On the other hand, an alteration of the action of the kidneys, although less apparent, may be equally interesting. The presence of albumin in the urine in human beings following chilling¹¹ presumably is a physiologic response.¹⁰ The development of albuminuria during hypothermia in animals,¹² as well as in human subjects, is probably a function of inadequate fluid intake. Albuminuria following dehydration may be observed in the absence of demonstrable renal damage; similarly its occurrence during hypothermia may be explained if the fluid intake is inadequate and the body is dehydrated.

Fluctuations in output of urine are related directly to fluid intake. If the intake is reduced, the hourly output is small; if the intake is large, the urine output is within the average range for normal subjects. A diminution in glomerular filtration and renal blood flow, however, has been an invariable accompaniment of hypothermia,¹³ irrespective of fluid intake. The concentration of waste products in the serum during hypothermia has varied in our series. In the patient under discussion (table 1), the concentration of nitrogenous products and phosphate increased appreciably during treatment. Shortly before death, the nonprotein nitrogen was 70 mg. per hundred cubic centimeters and urate was 11.5 mg. per hundred cubic centimeters. Serum phosphate reached a maximum of 6.1 mg. per hundred cubic centimeters

11. Schlomka, G.: Untersuchungen über den Einfluss äusserer Abkühlungen auf die Nierentätigkeit, *Ztschr. f. d. ges. exper. Med.* **61**:405, 1928.

12. (a) Zillessen, O. F. I.: Ueber Erkältung als Krankheitsursache, Inaug. Dissert., Marburg, 1899. (b) Lassar, O.: Ueber Erkältung, *Virchows Arch. f. path. Anat.* **79**:168, 1880. (c) Meyer-Lierheim, F., and Siegal, W.: Erkältung als Krankheitsursache, *Ztschr. f. exper. Path. u. Therap.* **9**:450, 1911. (d) Giese.^{7b}

13. Unpublished data.

forty-five hours after hypothermia was induced and shortly before death had decreased to 5 mg. per hundred cubic centimeters. The combination of decreased glomerular filtration and dehydration, undoubtedly, can be held responsible for these high values. Therapeutically, it is believed that little can be done to increase glomerular filtration during hypothermia, but dehydration can be combated effectively by an augmented fluid intake.

No morphologic changes were noted in the kidneys at the post-mortem examination of our patient. Few morphologic changes have been reported by others, either for animals or for human subjects. Giese^{7b} found no significant anatomic variations in rabbits which had shown albuminuria before death. Zillesen,^{12a} however, observed hyperemic glomeruli, areas of hyaline degeneration, cortical hemorrhages and hyaline and blood cell casts in the tubules. Smith⁶ was unable to demonstrate evidence of renal damage in human subjects.

The brain and meninges are not excepted from morphologic alteration during hypothermia, and extensive studies of such changes may contribute to an understanding of the effects on the psyche observed during and after hypothermia.^{3a} Nicolaysen,⁸ Peter¹⁴ and Bender¹⁵ have reported congestion of the meninges and an increased amount of cerebrospinal fluid in persons frozen to death. In 3 human subjects, Fay¹⁶ observed clinical evidence of cerebral edema after the body temperature returned to normal. In 1 spinal puncture showed a marked accumulation of fluid in the subarachnoid space. Evidence of cerebral edema was not apparent in our patient, although a few foci of cortical cell degeneration and fresh subependymal hemorrhages in the wall of the third ventricle were seen.

The other organs were essentially normal. The adrenal glands showed lipid depletion. Meixner¹⁷ expressed the belief that such a change was a direct result of hypothermia. Sano and Smith¹⁸ did not agree. The other endocrine glands, the pituitary, the thyroid and parathyroids and the gonads, have been reported in the literature as normal. Thrombosis of the veins following exposure to the cold has been noted

14. Peter, M.: Des températures basses excessives, *Gaz. hebd. de méd. et de chir.* **9**:499, 1872.

15. Bender, L.: Lesions in the Brain in Death Caused by Freezing, *Arch. Neurol. & Psychiat.* **20**:319 (Aug.) 1928.

16. Fay, T.: Observations on Prolonged Human Refrigeration, *New York State J. Med.* **40**:1351, 1940.

17. Meixner, K.: Ein Fall von Tod durch Erfrieren, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **18**:270, 1931.

18. Sano, M. E., and Smith, L. W.: A Critical Histopathologic Study of Fifty Postmortem Cases of Cancer Subjected to Local or Generalized Refrigeration as Compared to a Similar Control Group of Thirty-Seven Non-Refrigerated Cases, *J. Lab. & Clin. Med.* **26**:443, 1940.

and is discussed in current literature as a frequent complication of freezing. It has been observed, however, only in vessels of frozen parts of the body¹⁹ and not in parts that are not frozen. Thrombosis should not be considered as a complication of therapeutic hypothermia.

The small chromophobic adenoma within the pituitary gland was certainly noncontributory. It was not large enough to have altered the size of the sella turcica, as judged by roentgen ray examination. There was no clinical evidence that the patient was suffering from a adenoma of the pituitary body. It seems most unlikely that the adenoma was related to the patient's schizophrenia. Of some interest is the fact that the brain showed so few variations from normal. After eight years or profound mental disturbances only minimal demonstrable alterations in the morphologic structures were evident.

Several of the acid-base constituents of the blood in this patient (table 1), as well as in the other patients studied by us during hypothermia, have been discussed by Dill and Forbes.^{3b} The concentration of hemoglobin in the blood in patient W. D. showed a progressive increase during treatment. The oxygen capacity increased from 19.3 to 23.3 volumes per cent and the cell volume from 45 to 52 per cent. The oxygen saturation of arterial blood remained normal. The values of 100 per cent for saturation are high and are assumed to be technical errors. The shift toward acidosis was marked. At the end of forty-five hours the total carbon dioxide content of arterial whole blood had decreased from 46.5 volumes per cent to 17.5 volumes per cent. This reduction, measured at body temperature, occurred despite the fact that in vitro alkaline reserve increases with decreasing temperatures.^{3b} The lowest p_H observed was 7.22. Four known factors contributed to the diminished alkaline reserve, as follow: 1. Hyperventilation occurred during most of the period of treatment. Since hyperventilation alone produces an increase in p_H , it must be assumed that other factors were operating which counteracted the hyperventilation alkalosis. 2. The concentration of lactate was increased. The maximum value noted was 56.1 mg. per hundred cubic centimeters. Restlessness and increased muscular activity were largely responsible for this, although a disturbance of intermediary metabolism of carbohydrate has not been excluded.^{3b} 3. Phosphate and urate were retained. These changes have been discussed already. 4. The concentration of ketone bodies was increased. All specimens of urine contained acetone and ketone bodies. In summary, it may be stated that there are three major trends in the acid-base balance of patients during hypothermia,

19. Hodara, M.: Beitrag zur Histologie der Erfrierung, München. med. Wchnschr. 43:341, 1896. Kriege, H.: Ueber hyaline Veränderungen der Haut durch Erfrierungen, Virchows Arch. f. path. Anat. 116:64, 1889.

namely, concentration of blood, acidosis and retention of products usually excreted by the kidney.

In table 2 the data from the analyses of certain base constituents of tissue are compared with normal values.²⁰ In all tissues except heart muscle the concentration of water is less than normal. The sodium concentration is decreased and the potassium concentration increased in all. No constant change was noted regarding calcium. It is apparent that the tissues studied had lost water and sodium and had gained potassium. Depletion of interstitial fluid containing sodium and loss of cellular fluid leaving potassium behind could account for these variations.

SUMMARY AND CONCLUSIONS

Morphologic and metabolic data are reported for a patient who died during experimental hypothermia. The patient had suffered from schizophrenia for more than ten years but was physically sound. During hypothermia a minimum rectal temperature of 80 F. was observed. The temperature remained below 98 F. for fifty hours. During restoration of temperature external heat was applied too rapidly. Cardiovascular collapse ensued, and death followed shortly. An autopsy was performed four hours later. The significant anatomic findings included patchy bronchopneumonia, slight degeneration of the cortical cells of the brain and a small adenoma of the pituitary gland. It is believed that none of the morphologic changes was independently responsible for death.

In retrospect it is thought that sudden vasodilatation was responsible for the cardiovascular breakdown. This change was aggravated by a combination of sluggish circulation, bronchopneumonia, impaired gas exchange in the lungs, acidosis and diminished glomerular filtration in the kidneys. Death, therefore, was produced by functional, rather than anatomic, disturbances.

It is concluded that prolonged hypothermia is without serious morphologic effect on normal tissue.

20. Shohl, A. T.: *Mineral Metabolism*, New York, Reinhold Publishing Corporation, 1939.

THERAPY OF TETANUS

A STUDY OF TWO HUNDRED AND SEVENTY-SIX CASES

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In July 1933 a new routine for the treatment of patients with tetanus was introduced into the Cook County Hospital. In a previous publication¹ the rationale of this method of management has been discussed. This paper will be devoted to a description of the treatment employed and to a statistical analysis of the results noted in the care of 96 patients (referred to as the new series) managed according to the new routine during the seven year period ending in July 1940. Included as a basis for comparison is a discussion of the observations made from a detailed review of the hospital records of 180 patients (designated as the old series) treated according to the older routine during an eleven year period which preceded the introduction of the present method of management. Likewise, the general trend of the mortality from tetanus at Cook County Hospital has been reviewed for the years 1908 to July 1940 inclusive.

It is important to emphasize that the new technic stressed the centralization of control in the hands of a specially trained medical and nursing staff, which was drilled periodically in respect to the details of management. Practically all patients treated according to the new routine were placed under the care of special nurses during the major portion of their sojourn in the hospital.

SEDATIVE THERAPY

Mild tetanus was encountered in patients free from convulsions, moderately severe tetanus in patients without cyanosis during tetanic spasms and severe tetanus in patients with cyanosis as an integral phase of the convulsive seizures. The two chief apparent dangers incident to convulsions were death from acute asphyxia and development of aspira-

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The attending staff, the house physicians and the nursing staff of the Cook County Hospital gave constant cooperation and assistance. The Winthrop Chemical Company, Inc., supplied the avertin with amylene hydrate and Eli Lilly & Company the sodium amytal employed in this study.

1. Spaeth, R.: A Clinical Study of Tetanus, *Am. J. Dis. Child.* **60**:130-169 (July) 1940.

tion pneumonia. I did not investigate the incidence of compression fractures of the vertebrae, described by Dietrich.²

Although a dark, quiet environment and procedures to increase the patient's comfort were utilized, active sedative therapy was the keystone of treatment. Of the many sedative drugs discussed in the literature on tetanus, sodium amytal (sodium isoamylethylbarbiturate) and avertin with amylene hydrate (tribromethanol dissolved in amylene hydrate) were the ones used almost routinely since July 1933.

Both the nurses and the hospital physicians were permitted to administer sedative drugs for restlessness, painful spasticity of the skeletal muscles (neck, abdomen, trunk or extremities) or disturbing tonic spasms. Those in charge were instructed to use minimal effective doses in order to avoid depression of the cough reflex and the resultant danger of pneumonia. An attempt was made to keep the patient in a state of light to moderate narcosis until sedatives were no longer needed. The average patient required sedatives, usually in progressively diminishing amounts, for two or more weeks. When respiratory embarrassment occurred during convulsions, the attendants tried to determine whether the difficulty was caused by obstruction of the throat by secretions which could not be swallowed. Any such secretions were removed by mechanical means (see section on "General Management"), and cautious sedative treatment was then employed. Because the amount of sedative drug required proved to be a fairly reliable guide in formulating the prognosis, the nurses were instructed to make twenty-four hour summaries of the sedative therapy.

Printed instructions proved to be of considerable aid in facilitating treatment.³ To the record of each patient was attached a table indicating the number of cubic centimeters of 2.5 per cent stock solution of avertin with amylene hydrate equivalent to 100, 50, 25, 15 and 10 mg. of tribromethanol per kilogram of body weight. The amount of sodium amytal corresponding to 5 mg. per kilogram of body weight⁴ was found to be best expressed in milligrams, grains and cubic centimeters of 5, 10 and 20 per cent solutions, respectively.

2. Dietrich, H. F.: Tetanus in Childhood, *Am. J. Dis. Child.* **59**:693-710 (April) 1940.

3. These instructions have been considered in detail elsewhere.¹ On the routine forms, in addition to the data usually indicated, the following information is recorded: age; weight; previous serum or drug medication or idiosyncrasy; blood pressure; other diseases or complications (arteriosclerosis, edema, cachexia of any degree, acidosis, obesity, hepatic or renal disease).

4. Five milligrams per kilogram represents a dose corresponding to approximately $\frac{1}{25}$ grain (2.6 mg.) of drug per pound (0.45 Kg.) of body weight. The 240 mg. dose is contained in the $3\frac{3}{4}$ grain ampule and 480 mg. in the $7\frac{1}{2}$ grain ampule.

After an appropriate dose of avertin with amylene hydrate, given as a retention enema,⁵ a sedative action ordinarily appeared in five to ten minutes. For the average patient with tetanus the initial dose was a volume of stock solution providing 25 mg. of tribromethanol per kilogram of body weight, followed at fifteen to thirty minute intervals with 10 to 15 mg. per kilogram, in accordance with the needs of each individual patient. This initial dose was raised to 40 or 50 mg. of tribromethanol per kilogram when severe convulsions were present and reduced to 15 mg. per kilogram when convulsions were either absent or mild. Three precautions were found to be important: (1) keeping an adequate supply of stock solution on the treatment tray; (2) testing the solution with congo red before each administration of the drug,⁶ and (3) leaving the rubber tube in the rectum so that avertin with amylene hydrate could be administered without delay.

Sodium amytal was used alone or in conjunction with avertin with amylene hydrate. On the basis of past experience, an amount equivalent to 5 mg. per kilogram of body weight⁴ was found to be a safe initial dose, with an upper limit of 240 mg.⁴ for children and 480 mg. for adults. It was found desirable to try the effect of 240 mg. before resorting to a higher dose. The intramuscular injection of a 10 per cent aqueous solution, followed by additional doses at thirty to sixty minute intervals as needed, proved satisfactory for the patient with tetanus of average severity. Intravenous injections of a 5 to 10 per cent solution (1 cc. per minute—accurately timed!) were reserved for the control of alarming asphyxial spasms. The drug was given orally (dissolved in various pleasant vehicles) to those patients who were able to swallow, and it was administered rectally to those not in need of immediate narcosis but unable to swallow fluids with ease. Intravenous injections of sodium amytal induced the most prompt narcosis,⁷ intramuscular administration a slower response and both oral and rectal treatment the slowest reactions.

Table 1 summarizes the sedative treatment employed for 52 patients of the new series.

I observed no clinical evidences of toxic injury to the various body organs among those patients who recovered after being treated with

5. Avertin with amylene hydrate is given only in the form of a retention enema, whereas sodium amytal can be administered by any of the available channels.¹

6. When congo red is added to the stock solution, the appearance of a blue or violet color indicates the presence of a toxic dibromacetaldehyde, caused either by aging or by preparation of the solution with excessively hot water. Such material is not to be used. The test with congo red is dependable only when distilled water has been used as the diluent.

7. The intravenous injection is to be stopped as soon as the patient begins to show signs of drowsiness.

large doses of avertin with amylene hydrate or of sodium amytal. Likewise, no acquired resistance to either drug developed during the period of active treatment. However, in several of the patients who died convulsions persisted despite intensive therapy with sodium amytal or avertin with amylene hydrate. As might be anticipated, the more

TABLE 1.—*A Summary of Results of Treating Fifty-Two Patients with Tetanus by Means of Avertin with Amylene Hydrate and Sodium Amytal*

Age, Yr.	Weight, Kg.	Tribromethanol *					Sodium Amytal *				
		Maxi- mal Single Dose	Maxi- mal Daily Dose	Aver- age Daily Dose	Number of Days Given	Total Dose	Maxi- mal Single Dose	Maxi- mal Daily Dose	Aver- age Daily Dose	Number of Days Given	Total Dose
Patients Who Recovered											
12	40.9	50.0	321.0	245.6	17.0	417.6
12	37.0	6.5	53.3	26.7	8	214.0
8	25.0	7.7	53.7	21.5	10	215.0
8	24.0	10.0	40.0	28.0	5	140.0
5†	16.3	25.0	152.0	115.6	7.0	809.0	14.7	29.4	17.6	5	88.3
35	81.8	68.8	310.5	173.8	10.0	1,738.0	5.8	8.8	5.8	2	11.7
7	22.7	20.0	415.0	179.4	25.0	4,489.0	10.5	31.6	15.4	10	154.3
5	20.4	25.0	292.0	162.0	17.0	2,765.0	11.7	11.7	11.7	2	23.4
9	31.8	25.0	174.0	101.5	8.0	812.0
15	39.5	56.0	278.0	139.5	14.0	1,954.0
4	15.9	40.0	230.0	134.8	11.0	1,483.0	15.1	30.2	30.2	1	30.2
46†	68.2	20.0	125.0	74.7	17.0	1,270.0	7.0	21.1	11.3	13	147.8
49†	68.2	20.0	151.0	94.6	10.0	946.0	7.0	21.1	14.9	13	193.7
18†	63.6	25.0	135.0	63.8	21.0	1,342.0	7.6	22.7	6.1	12	73.7
11	36.3	23.0	354.0	205.7	13.0	2,674.0	6.6	26.4	18.6	11	204.5
13	38.2	15.0	262.0	125.5	11.0	1,380.0	6.2	36.4	24.0	19	457.4
7	20.0	25.0	365.0	235.3	12.0	2,824.0	3.2	6.4	6.4	4	25.6
43†	65.9	20.0	200.0	111.8	12.0	1,341.0	7.2	7.2	5.8	3	17.4
8†	27.3	35.0	217.0	112.2	22.0	2,469.0	17.5	17.5	13.0	4	52.1
10	29.5	25.0	200.0	116.6	12.0	1,405.0	4.3	10.8	9.7	3	29.2
34	75.4	25.0	241.0	131.0	7.0	916.0
21	62.0	25.0	174.0	113.0	10.0	1,132.0
45	66.0	50.0	194.0	161.0	8.0	1,288.0
Patients Who Died											
10	30.5	78.0	199.2	2.5	498.0
35†	71.8	80.0	194.9	127.4	9.0	1,147.0	6.7	13.8	11.1	6	67.7
13	37.5	107.0	272.0	3.0	816.0
6	18.2	80.0	583.0	487.3	55.0	2,680.0
30	81.8	125.0	334.0	304.0	1.5	456.0
13†	43.2	30.0	177.0	177.0	1.0	177.0	5.5	44.0	37.0	1.5	55.5
41†	65.9	25.0	200.0	188.0	2.0	375.0	7.2	21.8	21.8	1	21.8
7	25.0	45.0	351.0	296.0	4.0	1,185.0	9.6	19.2	19.2	1	19.2
11†	36.4	50.0	371.0	371.0	1.0	371.0	6.6	6.6	6.6	1	6.6
3	13.6	60.0	221.0	248.0	2.0	497.0
15	45.4	60.0	283.0	174.0	9.0	1,567.0
42†	77.3	60.0	306.0	263.3	3.5	939.0	3.1	3.1	3.1	1	3.1
56	72.7	60.0	116.0	155.3	1.5	233.0	4.9	9.9	9.9	1	9.9
20	63.6	58.0	196.0	202.6	1.5	304.0
28	69.5	25.0	283.0	277.5	2.0	555.0
6†	22.7	20.0	137.0	137.0	1.0	137.0	10.5	10.5	10.5	1	10.5
2.5	11.4	25.0	155.0	83.5	2.0	177.0	21.0	84.2	84.2	1	84.2
26†	72.7	25.0	305.0	295.5	2.0	591.0	6.6	16.5	16.5	1	16.5
19†	54.5	25.0	82.0	69.3	1.5	104.0	8.8	8.8	8.8	1	8.8
8†	25.0	25.0	292.0	260.0	1.5	390.0	9.6	19.2	19.2	1	19.2
13†	65.9	20.0	55.0	61.0	1.5	92.0	7.2	7.2	7.2	1	7.2
19†	59.1	20.0	241.0	145.6	8.0	1,165.0	4.0	24.3	24.3	1	24.3
59†	65.9	10.0	86.0	67.0	2.0	134.0	3.6	25.4	12.7	2	25.4
69†	70.5	10.0	56.7	56.7	1.0	56.7	3.4	20.4	20.4	1	20.4
36†	43.2	20.0	135.0	106.5	4.0	426.0	5.5	33.3	25.9	5	129.6
17†	60.4	15.0	250.0	175.4	5.0	877.0	7.9	11.9	10.7	6	64.6
32†	47.7	25.0	258.0	246.6	1.5	370.0	10.0	10.0	10.0	1	10.0
6	25.0	25.0	350.0	248.7	4.0	995.0
41	77.3	25.0	213.0	191.6	3.0	575.0

* All doses are expressed in terms of milligrams per kilogram of body weight.

† Patients thus designated received both drugs on corresponding days during the major part of the illness. All others were given only one of the sedatives (at times with relatively small amounts of the other) during any given twenty-four hour period.

severely ill patients received the higher doses of the sedative drugs. This fact, among others, accounts for the observation that among the patients considered in table 1 approximately 35 per cent of those who died, in contrast to 10 per cent of those who recovered, had received single doses of avertin with amylene hydrate in excess of 50 mg. of tribromethanol per kilogram of body weight. In similar fashion, it explains why of the patients included in table 1, 42 per cent of those who died, in contrast to 15 per cent of those who recovered, had received

TABLE 2.—*An Analysis of Sedative Therapy for Two Hundred and Seventy-Six Patients with Tetanus*

Sedatives		Intensity of Disease						All Intensities	
		Mild		Moderate		Severe			
		Recov- ery	Death	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death
Old series	Morphine sulfate alone *....	4	..	1	..	1	19 (2)†	5	19
	Morphine sulfate, chloral hydrate and bromides....	13	..	6	3	1	23 (2)	20	26
	Morphine sulfate, chloral hydrate and phenobarbital.....	3	..	2	5	..
	Morphine sulfate, chloral hydrate and magnesium sulfate.....	1	1	..	12	1	13
	Chloral hydrate and bromides.....	4	..	5	1 (1)	2	9	11	10
	Miscellaneous †.....	1	..	6	5 (1)	7	5
	None or negligible.....	7	..	5	3 (1)	2	41 (2)	14	44
	Total.....	32	..	26	8	5	109	63	117
New series	Avertin with amylene hydrate *.....	6	..	16 (1)	..	3	15 (9)§	25	15
	Sodium amytal alone *.....	6	..	3	..	3 (1)	..	12	..
	Avertin with amylene hydrate and sodium amytal*	1	..	10	1#	5 (2)	17 (12)	16	18
	Miscellaneous ¶.....	3	..	1	4	..
	None.....	5	1 (1)	5	1
	Total.....	21	..	30	2	11	32	62	34

* For some patients negligible amounts of other sedatives were also used.

† The figure in parentheses indicates the number of patients with pneumonia.

‡ Magnesium sulfate, phenobarbital, codeine, barbitol were used alone or in various combinations.

§ A 6 year old boy had bilateral bronchopneumonia and septic parotitis which did not respond to intravenous injections of sodium sulfapyridine and type-specific antipneumococcus serum.

A 60 year old man had a markedly irregular heart for which digitalis was prescribed.

|| A 19 year old woman had pneumonia, septic parotitis and a septic abortion. A 59 year old man had pneumonia, marked stomatitis and evidence of neglect preceding hospitalization. In a 41 year old man the blood gave chemical evidence of moderate nonprotein nitrogen retention (53.3 mg. of urea nitrogen and 3.3 mg. of creatinine per hundred cubic centimeters of blood).

¶ Phenobarbital, codeine, morphine and chloral hydrate were used alone or in various combinations.

an average daily dose of avertin with amylene hydrate in excess of 200 mg. of tribromethanol per kilogram of body weight. Although the data embodied in table 1 do not enable one to establish definitely the relation between the amount of sedation and the clinical outcome, observation of the patients impressed me with the thought that both overzealous and inadequate sedative treatments were to be avoided. It

appeared that the so-called happy medium had to be determined for each individual patient.

In table 2 data for the new series and the old series are compared in terms of the sedatives employed. Although table 2 is self explanatory, certain facts are worthy of emphasis. 1. Sedative therapy was of little importance, except from the standpoint of comfort, for those patients with mild forms of tetanus. Nevertheless, because of the difficulty of predicting the course of the disease, all patients with tetanus should receive routine sedation in accordance with individual needs. 2. Sodium amytal and avertin with amylene hydrate appeared to be definitely superior to the sedatives previously used for the treatment of moderate and severe tetanus. 3. In cases of severe tetanus, sodium amytal and avertin with amylene hydrate frequently failed to prevent death.⁸ 4. Complications (pneumonia, septic parotitis) and associated pathologic conditions (septic abortion, cardiac abnormality, etc.) must be considered in comparing the recovery rates obtained in response to the different sedatives employed.

SERUM THERAPY

Table 3 shows that tetanus antitoxin was administered to all except 13 patients. Serum treatment was omitted for 2 patients of the new series because they were convalescing at the time of hospitalization, and 11 patients of the old series died before antitoxin could be injected.

Tables 4 and 5 summarize the results of serotherapy.

In another publication⁹ I have analyzed the foregoing data on a clinical and immunologic basis. The results of this analysis⁹ indicated that a single dose of 30,000 American units probably represents an adequate amount of tetanus antitoxin for general use in all age groups.

8. Dietrich² has described favorable results in treating tetanus with seconal (sodium propylmethylcarbonylallylbarbiturate). The technic of seconal therapy has been presented by Breslow and Poncher (Use of Seconal in Pediatric Procedures, Illinois M. J. **80**:210-212 [Sept.] 1941). Curare and curarine have been used with some encouraging results in treating convulsions and spastic states (Melzner, E.: Experimentelle Untersuchungen über die Behandlung des Wundstarrkrampfes mit einer Kombination von Curarin und Avertin, Deutsche Ztschr. f. Chir. **212**:308-324, 1928. Cole, L.: Tetanus Treated with Curare, Lancet **1**: 475-477 [Sept. 1] 1934. Mitchell, J. S.: A Case of Tetanus Treated with Curarine, *ibid.* **1**:262-264 [Feb. 2] 1935. West, R.: Intravenous Curarine in the Treatment of Tetanus, *ibid.* **1**:12-16 [Jan. 4] 1936. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**:307-327 [Feb.] 1939. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**:322-324 [Jan. 27] 1940).

9. Spaeth, R.: Serum Therapy of Tetanus, with Special Reference to the Course of Antitoxin Titers in the Blood After Treatment with Specific Serum, Am. J. Dis. Child. **61**:1146-1174 (June) 1941.

TABLE 3.—*The Routes Employed for Administration of Antitoxin to Two Hundred and Seventy-Six Patients with Tetanus*

Severity of Disease	Series	Unknown		None		Intra-thecal *		Intra-muscular		Intra-venous		Intramus-cular and Intravenous		All Routes	
		Recovery		Recovery		Recovery		Recovery		Recovery		Recovery		Recovery	
		Death	Death	Death	Death	Death	Death	Death	Death	Death	Death	Death	Death	Death	Death
Mild	Old	29	3	..	32	..
	New	2†	4	..	6	..	9	..	21	..
Moderate	Old	1	1	..	1	21	6	1	26	8
	New	1‡	3	1	12	..	11	1	30	2
Severe	Old	10	4	78	..	3	..	4	1	14	5	109
	New	1§	1	..	7	20	3	11	11	32
Total	Old	1	1	..	11	57	84	..	3	1	4	4	14	63	117
	New	1	..	2	1	8	1	25	20	26	12	62	34

* This category includes all patients who received antitoxin by the intraspinal or intracisternal routes, either alone or in combination with other channels.

† Convalescent patients, admitted on the fourteenth and the fifteenth day of the disease.

‡ The patient received 30,000 units by unstated routes over four days preceding hospitalization and was given 40,000 units intramuscularly on the day of admission to the hospital.

§ On the day of hospitalization the referring physician had administered 20,000 units intraspinally.

TABLE 4.—*The Average Doses of Antitoxin Employed in Treatment of One Hundred and Sixty-Nine Patients of Old Series with Tetanus*

Intensity of the Signs of Tetanus	First 24 Hours				First 48 Hours				Entire Stay in Hospital *			
	Recoveries		Deaths		Recoveries		Deaths		Recoveries		Deaths	
	Pa-tients Dose†		Pa-tients Dose		Pa-tients Dose		Pa-tients Dose		Pa-tients Dose		Pa-tients Dose	
	Pa-tients	Dose	Pa-tients	Dose	Pa-tients	Dose	Pa-tients	Dose	Pa-tients	Dose	Pa-tients	Dose
Mild.....	32	37,700	32	48,200	32	91,000
Moderate.....	26	35,200	8	41,400	23	56,100	6	73,500	26	119,400	8	103,900
Severe.....	5	31,200	98	37,000	5	43,200	36	66,200	5	78,200	98	55,400
All patients...	63	35,800	106	37,400	60	50,800	42	56,800	63	101,700	106	58,100

* The average number of days of serum treatment was five and three-tenths for those patients who recovered and one and eight-tenths for those who died (the average duration of life among those who died was two and one-tenth days).

† Serum had been injected by a number of routes (table 3). All doses are expressed in units.

TABLE 5.—*The Relation Between Dose of Antitoxin* and Clinical Outcome for Ninety-Two Patients of New Series Given All Serum Intramuscularly or Intravenously*

Dose of Antitoxin, Thousands of Units	Intensity of Disease				All Intensities		
	Mild to Moderate		Severe		Recovery	Death	Recovery Death
	Recovery	Death	Recovery	Death			
100,000	9 (1)†	1	2	6 (4)‡	11	7	1.5
81,000-90,000	1	1
71,000-80,000	9 (1)	..	6 (2)	5 (4)§	15	5	3.0
61,000-70,000	2	..	1	..	3
51,000-60,000	9	..	2	12 (7)	11	12	0.9
41,000-50,000	3	1 (1)	..	1 (1)	3	2	1.5
31,000-40,000	11	7 (4)	11	7	1.5
21,000-30,000	2	2
20,000	2	2

* All antitoxin was injected during the first twenty-four hours of hospitalization, except in the cases of 2 patients who received the total amounts over two to three days. Only 1 death occurred among the 17 patients first given serum after the fourth day of the disease.

† The figure in parentheses indicates the number of patients with pneumonia.

‡ A 60 year old man had a markedly irregular heart, and a 19 years old woman had septic parotitis, pneumonia and a septic abortion.

§ A 6 year old boy had septic parotitis and pneumonia, and a 59 year old man had pneumonia, marked stomatitis and evidences of extreme deprivation and neglect.

In order to allow a liberal margin of safety, a dose of 60,000 units was considered satisfactory for patients admitted to the hospital for serotherapy during the first five days of the disease and 40,000 units for mildly to moderately ill patients first treated later (see section on "results"). The analysis⁹ further indicated that single doses of these magnitudes, administered by the intravenous or the intramuscular route, were associated with antitoxin titers which were adequate, both in level and in duration, to meet the indications imposed by a rational method of specific serotherapy.

As noted in table 3, intrathecal serotherapy was emphasized in the old series and intravenous and intramuscular serotherapy in the new series. The percentage distribution of patients of the old series and of the new series, respectively, in terms of the routes of serotherapy was: (1) intrathecal, alone or with other channels, 78.3 and 1.0; (2) intravenous, with or without the intramuscular route, 12.8 and 86.4 and (3) intramuscular alone, 1.7 and 9.4. Seven patients (3.9 per cent) in the old series received antitoxin intracisternally.

Among those patients of the old series given intrathecal serotherapy, the following results were noted: 1. Fifty-seven (40.4 per cent) of 141 patients recovered. 2. All of the 29 patients with mild forms of tetanus recovered. 3. Among those with moderately severe illness 24 (80 per cent) of 30 recovered. Intrathecal serotherapy obviously contributed directly to the unfavorable outcome for 2 patients who died. One of these patients was first hospitalized and given specific serum by the intramuscular and intravenous routes on the ninth day of his illness. The intraspinal injection of 20,000 units of tetanus antitoxin on the following day was succeeded by the rapid onset of marked generalized rigidity and convulsions, and the patient died on the eleventh day of illness. Severe convulsions developed in the other patient promptly after the intraspinal administration of 40,000 units, and the patient died ten hours after admission to the hospital. 4. Of the patients who were severely ill, only 4 (4.5 per cent) of 82 recovered. Intraspinal treatment apparently initiated convulsions in at least 5 of those who died. Another patient presented a picture of shock after the intracisternal injection of tetanus antitoxin on the fifth day of hospitalization (fourteenth day of tetanus) but ultimately recovered. 5. Apparently death could be caused by spinal or cisternal punctures per se. Acute, fatal asphyxial spasms occurred in 3 patients during the performance of spinal punctures and in 1 patient during the introduction of a needle into the cistern. In summary, the evidence would indicate that cisternal and spinal punctures and the introduction of antitoxin into the subarachnoid spaces may be classified as adverse environmental disturbances, which may be tolerated by the mildly to moderately severely ill patients but not by those with more severe forms of tetanus.

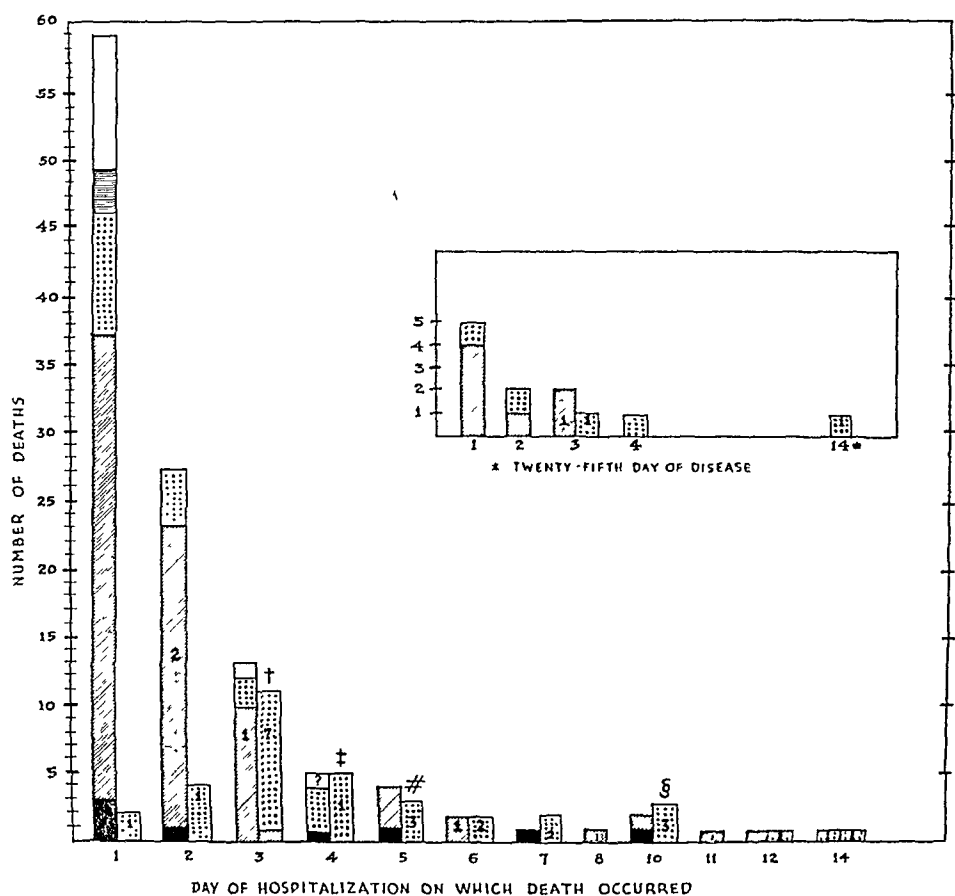
When antitoxin was introduced intravenously, either alone or in combination with intramuscular injection, the following results were noted: 1. Five (21.7 per cent) of 23 patients of the old series and 33 (61.4 per cent) of 83 patients of the new series recovered. 2. All of those with mild forms of tetanus recovered. 3. Among the patients with moderately severe tetanus only a single death occurred, 27 (96.4 per cent) of 28 patients of this group having recovered. 4. Recovery occurred in only 1 (5.3 per cent) of 19 severely ill patients of the old series, in contrast with 10 (24.4 per cent) of 41 patients of the new series. Intravenous serotherapy apparently caused no deaths and did not in any recognized instance adversely influence the ultimate clinical status of the patients thus treated.

Obviously, the limited number of patients given serum exclusively by muscle precludes any conclusions concerning the value of this type of management. Aside from the fact that all 3 of the severely ill patients of the old series died, and only 1 of 5 patients of the new series (4 moderately ill, 1 severely ill), it is of interest that 1 severely ill patient of the new series recovered after receiving a single intramuscular injection of 80,000 units. If one compares the intravenous and the intramuscular route for serum therapy in terms of safety, equipment and time required, degree of technical skill needed and relative speeds of absorption, the advantages of the former route are more theoretic than real. It is to be emphasized, however, that rapid absorption after intramuscular injection is facilitated by using the muscles on the anterolateral aspect of the thigh (not the gluteal region!) and possibly by giving one half of the total dose on each side.

In the chart I have analyzed the fatalities in terms of the day of hospitalization and the day of serum treatment¹⁰ on which death occurred, the route employed for the administration of tetanus antitoxin and the incidence and character of complications which might have contributed directly to the unfavorable outcome. It is of interest that approximately 50 per cent of the deaths in the old series occurred during the first day of hospitalization, 23 per cent on the second, 11 per cent on the third and the rest on the fourth to the fourteenth day. It is significant that of the 59 patients who died on the first day in the hospital, 3 had been given serum exclusively by the intramuscular route and 10 had received no serum. In the latter group, death occurred from fifteen minutes to eight hours after hospitalization, apparently as a consequence of asphyxial spasms. At least 2 of these patients presented the clinical picture

10. The day of hospitalization for the treatment of tetanus corresponds to the day of serum treatment, except in the cases of 16 patients, 11 of whom received no antitoxin and 5 of whom received antitoxin after a delay of twenty-four hours or less.

described by Dietrich,² namely, coma, shock, rapid stertorous respirations and terminal disappearance of convulsions. I have observed the onset of similar clinical pictures in patients with tetanus who were sub-



The relation between the routes of serotherapy and the time of death for 145 patients with tetanus. The large chart includes all patients and the inset only those who were hospitalized for treatment after the fourth day of the disease.¹⁰ The first column for any day or any single column represents patients of the series from 1921 to July 1933, and the second column represents patients of the series from July 1933 to July 1940. The routes by which antitoxin was administered are indicated as follows: solid black, intracisternal; diagonal lines, intraspinal (in some cases accompanied by injection through another route); dots, intravenous; horizontal lines, intramuscular; white space, no serum injected, and white space with a question mark, route not stated. A numeral enclosed in a part of a vertical column indicates the number of instances of pneumonia among patients given antitoxin by the corresponding route. The symbols on the large chart bear the following significance: †, a 59 year old man had pneumonia and stomatitis and showed evidences of marked neglect preceding hospitalization; ‡, a 41 year old man had blood which gave chemical evidence of moderate retention of nonprotein nitrogen (53.5 mg. of urea nitrogen and 3.3 mg. of creatinine per hundred cubic centimeters of blood), and a 60 year old man had a markedly irregular heart for which digitalis was prescribed; #, a 6 year old boy had septic parotitis and bilateral pneumonia which failed to respond to specific antipneumococcus serum and intravenous injections of sulfapyridine, and, §, a 19 year old woman had pneumonia, septic parotitis and a septic abortion.

jected to such environmental disturbances as venoclysis, noise and bathing. In respect to the time of onset of death, it is noteworthy that approximately 82 per cent of the deaths in the new series occurred on the third to the fourteenth day of hospitalization, that serum had been administered intravenously to all except 1 of the patients and that potentially fatal complications were present in 22 patients (65 per cent) of this series. These facts are pertinent because Dietrich² has pointed out that all of the 13 deaths in his series occurred within thirty-six hours of intraspinal or intravenous serum treatment. In summary, therefore, the evidence as presented by the patients treated at the Cook County Hospital, as well as elsewhere,¹ indicates that intrathecal, but not intravenous, serum treatment may occasion the alarming clinical pictures described by Dietrich.² Nevertheless, the possibility of ill effects from intravenous serotherapy (including acute reactions of an allergic character) must not be dismissed, and the probable adequacy of intramuscular serum treatment is deserving of more widespread study.

For intravenous administration, the antitoxin was poured into a flask containing 500 to 1,000 cc. of diluent (5 per cent dextrose in physiologic solution of sodium chloride or in Hartmann's solution [sodium lactate in Ringer's solution, available commercially]) and was allowed to flow at a rate of about 60 drops per minute.¹¹ With but occasional exceptions, sensitivity tests were omitted.¹² The vast majority of the patients of the new series received, about thirty minutes before the antitoxin, a hypodermic injection of atropine sulfate and epinephrine hydrochloride (1:1,000), in accordance with the following schedule of doses:

Drug	Age of Patient			
	6 Mo.	2 Yr.	5 Yr.	Adult
Epinephrine hydrochloride (1:1,000)	3 minims (0.18 cc.)	4 minims (0.25 cc.)	5 minims (0.31 cc.)	8 minims (0.49 cc.)
Atropine sulfate	$\frac{1}{800}$ grain (0.12 mg.)	$\frac{1}{250}$ grain (0.24 mg.)	$\frac{1}{200}$ grain (0.3 mg.)	$\frac{1}{100}$ grain (0.6 mg.)

A syringe containing 1 cc. of epinephrine hydrochloride (1:1,000) was always available to treat any acute serum reaction. On certain occasions, 0.5 to 1.0 cc. of epinephrine hydrochloride (1:1,000) was poured into the solution of antitoxin.

11. Suggestions for a routine of serotherapy have been presented elsewhere.¹ The desirability of immersing the bottle of serum for about fifteen minutes in lukewarm water (not above 100 F. [37.7 C.]) has been pointed out by Hoyne (personal communication to the author) and the dangers incident to the use of improperly heated serum have been stressed (Hoyne, A. L.: *The Pharmacopeia and the Physician: Immunologic Methods in Pediatrics*, J. A. M. A. **112**:1581-1584 [April 22] 1939).

12. A complete discussion (theory and practice) of this problem has been presented in a previous publication.¹

When patients in the new series received antitoxin both by muscle and by vein, from one half to two thirds of the total dose was given by the latter route and one half of the total intramuscular dose was injected into the muscles on the anterolateral aspect of each thigh on the theory that absorption would be more rapid from two intramuscular depots than from one.

In 5 patients of the new series acute reactions occurred after the intravenous injection of 40,000 to 60,000 units of antitoxin. In the old series such reactions appeared in 2 patients after the intravenous administration of 4,000 and 20,000 units, respectively.¹³ Chills occurred in 2 patients, convulsions in 2, urticaria in 4, shock in 1, dyspnea in 4, nausea in 1 and fever (with a temperature of 104 to 105 F.) in 2. Of those with acute reactions, 1 patient in each series died. In neither instance, however, could the death be attributed to the acute reaction.¹⁴ The reactions were treated in accordance with accepted methods, namely, injections of epinephrine hydrochloride (1:1,000), elevation of the foot of the bed, maintenance of body warmth by the use of blankets and other safe sources of external heat and control of cyanosis and apnea by artificial respiration, inhalation of oxygen and respiratory stimulants as indicated.

In the new series, in 18 of 69 patients (7 deaths) who lived seven or more days after their first serum treatment, serum sickness developed five to thirteen days later. The records indicate that 19 of 63 patients¹⁵ of the old series who recovered showed signs of serum sickness six to fourteen days after the first injection of antitoxin. Twenty-eight (75.7 per cent) of all the late reactions appeared six to ten days, 5 (13.4 per cent) four to five days and 4 (10.9 per cent) eleven to fourteen days after the first dose of serum. Tables 6 and 7 reveal the following facts: 1. In the old series the incidence of late serum sickness showed yearly variations from zero to 85.7 per cent. In the new series the incidence during the period after January 1937 was approximately one-third that noted during the preceding three and one-half years and about one-half that recorded for the interval described in table 6. One can merely con-

13. Two other patients who died (1 after 300, and the other after 2,000, units of tetanus antitoxin had been administered intravenously) were not listed as dying of anaphylaxis, because the acute asphyxial spasms of tetanus obviously were responsible for the unfavorable outcomes.

14. The death in the new series was that of a 6 year old boy, who died of bronchopneumonia. Wheals and dyspnea developed in a 15 year old boy (old series) shortly after the intravenous injection of 4,000 units, but apparently he died of inadequately treated tetanic spasms (tetanus!).

15. In only 7 of the fatal cases in the old series did the patient survive the minimal period during which delayed serum sickness ordinarily occurs. For this reason, only the recoveries have been considered in this analysis.

jecture concerning the extent to which the use of more highly refined serum caused this lowered incidence. 2. Only 1 of 8 patients given anti-toxin by muscle, in contrast to 17 of 52 who received it by vein (table 7), experienced a late serum reaction. Although this is suggestive, the limited number of cases does not warrant the conclusion that intramuscular serotherapy reduces the incidence of late serum sickness.

TABLE 6.—*The Occurrence of Delayed Serum Reactions Among the Sixty-Three Patients of the Series from 1921 to July 1933 Who Recovered**

	1921	1922	1925	1926	1927	1928	1929	1930	1931	1932	1933†	Entire Period
Patients.....	10	11	8	2	3	5	4	5	3	7	5	63
Reactions.....	2	2	2	..	1	..	1	3	1	6	1	19
Percentage.....	20.0	18.2	25.0	..	33.3	..	25.0	60.0	33.3	85.7	20.0	30.1

* The average dose of antitoxin was 101,700 units. Fifty-nine of the 63 patients received over 40,000 units, and only 4 received less than this dose. Fifty-seven had received serum by the intraspinal route alone or in combination with other routes, 5 by the intravenous route alone or in conjunction with the intramuscular route and 1 by a route not described in the hospital record.

† January to July, inclusive.

TABLE 7.—*The Occurrence of Delayed Serum Reactions Among Sixty Patients of the Series from July 1933 to July 1940 Who Recovered*

Total Dose, Units	Route	July 1933 to December 1936			January 1937 to July 1940			Entire Period of Study		
		Pa-tients	Reac-tions	Per-centage	Pa-tients	Reac-tions	Per-centage	Pa-tients	Reac-tions	Per-centage
Over 40,000	Intravenous	19	10	52.6	26	3	11.5	45	13	28.8
	Intramuscular	2	1*	50.0	2	1	50.0
	Total.....	19	10	52.6	28	4	14.8	47	14	29.8
40,000 or less	Intravenous	3	2	66.6	4	2	50.0	7	4	57.1
	Intramuscular	3	3	6
	Total.....	6	2	33.3	7	2	28.5	13	4	30.7
All doses	Intravenous	22	12	54.5	30	5	16.6	52	17	32.7
	Intramuscular	3	5	1	20.0	8	1	12.5
	Total.....	25	12	48.0	35	6	17.1	60	18	30.0

* Sixty thousand units was administered intramuscularly.

3. The data contained in tables 6 and 7 do not enable one to establish any relation between the total dose and routes of serotherapy, on the one hand, and the incidence of late serum sickness, on the other.

The exacerbation of convulsions in 3 patients at the time of late serum sickness called attention to the importance of adequate treatment of the discomfort by topical application of antipruritic agents, supplemented by the oral administration of ephedrine compounds (ephedrine-amytal and ephedrine-seconal capsules are commercially available) and parenteral injections of epinephrine hydrochloride (1:1,000) as indicated.

TREATMENT OF THE LOCAL LESIONS

Tables 8 to 10 represent a study of the relation of the type of treatment of the local lesion to the respective mortality rates. They all show that no remarkable or consistent relation existed between the method of management of the local lesion and the clinical outcome. Those instances

TABLE 8.—*The Relation of the Care of Local Lesions and Mortality*

	Old Series (1921 to July 1933)		New Series (July 1933 to July 1940)	
	Recovery	Death	Recovery	Death
No surgical intervention				
Hot compresses (boric acid or plain).....	8	8	17	12
Cleansing of wounds, with or without local application of antiseptics *	2	10	3	4
Antiseptic dressings or irrigations †.....	5	7	2	2
Sulfanilamide, parenterally (abortion).....	1	..
Dry heat (gangrene of feet).....	..	1
Total.....	15	26	23	18
	(63.4)†		(43.8)	
Surgical intervention				
Drainage of purulent collections.....	3	8	2	..
Removal of splinters and slivers.....	..	5	3	..
Extraction of bullet.....	..	1
Exploration of suspected lesion, with or without local application of antiseptics *.....	7§	9	1	2
Removal of surface of wound, with or without local application of antiseptics *.....	2	..
Treatment of compound fractures.....	..	2
Miscellaneous procedures	2#	4	..	1¶
Total.....	12	29	8	3
	(70.7)		(27.3)	
No treatment recorded				
Lesion absent or indeterminate.....	10	7	7	3
Partial or complete healing of lesion noted.....	15	10	18	3
Innocent-appearing lesion	7	3	6	2
Lesion relatively inaccessible.....	2**	3††
Exceedingly rapid onset of death.....	..	30	..	1
Reasons not apparent.....	2	9	..	4
Total.....	36	62	31	13
	(63.3)		(29.5)	

* The antiseptics used include tincture of iodine, boric acid, diluted solution of sodium hypochlorite U. S. P., hydrogen peroxide and ethyl alcohol.

† The antiseptics used include hydrogen peroxide, solution of potassium permanganate and diluted solution of sodium hypochlorite.

‡ The figure in parentheses represents the per cent mortality.

§ Concentrated phenol was applied locally in 1 case.

The treatment for the 2 patients, respectively, was (a) wide resection of an infected abrasion, followed by cauterization with pure phenol, (b) resection of the gangrenous portion of an infected toe, followed by the application of dressings soaked with diluted solution of sodium hypochlorite.

|| The treatment for the 4 patients, respectively, was (a) excision of an infected puncture wound; (b) drainage of an infected palmar lesion which followed a toy pistol wound, with postoperative cauterization with phenol; (c) removal of the necrotic tissue from gangrenous feet and legs, with the postoperative use of petrolatum gauze, compresses soaked with diluted solution of sodium hypochlorite and dry heat (heat cradle), and (d) debridement of an inflamed purulent wound of the leg.

¶ Treatment included the debridement of inflamed puncture wound of leg; probing of lesion; boric acid compresses.

** Appendectomy wound and abortion, respectively.

†† Herniotomy, cholecystectomy and hemorrhoidectomy, respectively.

in which operative treatment apparently reduced the mortality rate (for lacerations and cuts [table 9] and for severe tetanus among patients of the new series [table 10]) lack statistical significance because of the small number of patients available for study. Table 9 justifies the follow-

ing statements: 1. The mortality from penetrating wounds was high in the old series but not in the new. Lacerations and cuts caused a high mortality in both series. In the old series tetanus which occurred post-operatively and after compound fractures was associated with the highest

TABLE 9.—*The Relation of Local Lesions and the Type of Treatment to Mortality*

Lesion	Series	Number of Patients	Percentage of All Patients	Number of Deaths	Percentage of All Deaths	Percentage Mortality	No Surgical Intervention		Surgical Intervention		No Treatment	
							Recovery	Death	Recovery	Death	Recovery	Death
Compound fracture	Old	7	3.9	7	6.0	100.0	2	2	3
	New	1	1.0	1
Postoperative lesion *	Old	6	3.3	5	4.3	83.3	2	1	3
Penetrating wound *	Old	74	41.1	54	46.1	73.0	3 (70.0)†	7	7 (74.1)	20	10 (73.0)	27
	New	27	28.1	7	20.5	25.9	4 (50.0)	4	6 (14.3)	1	10 (16.6)	2
Laceration or cut	Old	32	17.8	22	18.8	68.7	2 (80.0)	8	4‡ (43.0)	3§	4 (73.3)	11
	New	22	22.9	11	32.3	50.0	4 (55.5)	5	2	7 (36.3)	4
Miscellaneous lesions *	Old	24	13.3	15	12.8	62.5	5 (54.5)	6	2	4 (63.6)	7
	New	16	16.7	7	20.5	43.7	6 (45.4)	5	1	..	2 (50.0)	2
Superficial lesion *	Old	13	7.2	5	4.3	38.4	3	..	1	1	4 (50.0)	4
	New	15	15.6	5	14.7	31.2	6 (33.3)	3	1	..	3 (40.0)	2
Lesion absent or indeterminate	Old	17	9.4	7	6.0	34.2	10 (41.2)	7
	New	10	10.4	3	9.0	30.0	7 (30.0)	3
Infection of unknown cause	Old	7	3.9	2	1.7	28.5	2	1	1	3	..
	New	5	5.2	1	3.0	20.0	2	1	2	..
All lesions	Old	180	99.9	117	100.0	65.0	15 (63.4)	26	12 (70.7)	29	36 (63.3)	62
	New	96	99.9	34	100.0	35.4	23 (43.8)	18	8 (27.3)	3	31 (29.5)	13

* Under this category are included the following lesions:

	Old Series		New Series			Old Series		New Series	
	Recov-ery	Death	Recov-ery	Death		Recov-ery	Death	Recov-ery	Death
Penetrating wounds caused by					Postoperative lesions				
Nail.....	9	23	12	..	Appendectomy....	1
Tack.....	..	2	1	..	Cholecystectomy..	..	1
Sliver, splinter....	4	10	6	2	Hernioplasty.....	..	1
Gunshot.....	2	6	..	1	Hemorrhoidectomy	..	1
Blank cartridge....	1	11	Amputation of leg	..	1
Firecracker.....	3	..	1	..	Reoperation, frac- ture.....	..	1
Fence picket.....	1					
Rusty wire.....	1	Miscellaneous lesions				
Clothes hanger....	1	Burn.....	2	5	3	1
Cinder, gravel....	..	2	..	1	Osteomyelitis.....	..	1
Garden rake.....	1	Carbuncle.....	1 ^a
Unknown cause....	..	1	Furuncle.....	..	1
Superficial lesions					Crushing injury...	5	4	4	2 ^b
Scratch.....	1	3	2	2	Gangrene (leg)....	..	3	1	2
Bruise.....	6	1	7	3	Vaccination.....	1	1
Blister.....	1	1	1	..	Abortion.....	1	..	1 ^c	1

a. The patient was addicted to morphine, and the lesion was caused by repeated hypodermic injections.

b. In 1 case the injured leg had been amputated before the onset of tetanus.

c. Sulfanilamide was administered parenterally in treatment.

† The figure in parentheses represents the per cent mortality.

‡ Three patients had mild and 1 patient had moderately severe tetanus.

§ All patients had severe tetanus.

fatality rates. 2. The old series contained approximately 50 per cent more patients with penetrating wounds than did the new. On the other hand, the percentage incidence of superficial lesions (with relatively low

mortality) in the new series was twice that noted in the old. 3. For any type of treatment of specific local lesions, the mortality rates were consistently lower in the new series than in the old.

Table 10 indicates that the severity of the tetanus (enhanced by the presence of complications or other adverse conditions), and not the method of treatment of the local lesions, apparently determined the clinical outcome.

Personal observation of the patients of the new series stimulated the thought, previously entertained,¹ that surgical treatment of the local

TABLE 10.—*The Relation of the Severity of Tetanus and the Care of Local Lesions to Mortality*

Severity of Tetanus	Series	No Surgical Intervention		Surgical Intervention		No Treatment		All Treatments	
		Recov- ery	Death	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death
Mild.....	Old	5	..	8	..	19	..	32	..
	New	9	..	1	..	11	..	21	..
Moderate.....	Old	9 (10.0)*	1†	3 (40.0)	2‡	14 (26.3)	5§	26 (23.5)	8
	New	10 (16.6)	2#	4	..	16	..	30 (6.2)	2
Severe.....	Old	1 (96.1)	25	1 (96.4)	27	3 (95.0)	57	5 (95.6)	109
	New	4 (80.0)	16	3 (50.0)	3	4 (76.4)	13	11 (74.4)	32
Total.....	Old	15 (63.4)	26	12 (70.7)	29	36 (63.2)	62	63 (65.0)	117
	New	23 (43.8)	18	8 (27.3)	3	31 (29.5)	13	62 (35.4)	34

* The figure in parentheses represents the percentage mortality.

† A 47 year old man with an infected burn treated with diluted solution of sodium hypochlorite and boric acid solution (intraspinal serotherapy, inadequate sedation).

‡ A 5 year old boy from whose foot a piece of wood was removed (death during asphyxial spasm, intraspinal serotherapy) and a 48 year old man with an infected nail puncture wound of foot, which was opened twice while the patient was in the hospital (death from bronchopneumonia on the fifteenth day of hospitalization).

§ The lesions were absent in 1 patient, minor (superficial crusts) in 2, a healed puncture wound in 1 (wood removed before hospitalization) and a laceration in 1. The patients' ages were 78, 75, 63, 44 and 34 years. Pneumonia was noted in 2 patients (aged 78 and 34). Sedation was inadequate in 4, and 3 had received intraspinal serotherapy.

A 39 year old man with superficial injuries of the hand treated with hot dressings (death on the fourteenth day of hospitalization, bronchopneumonia, history of chronic alcoholism), and a 60 year old man with gangrene of the feet treated by heat cradle (death on fourth day of hospitalization, markedly irregular heart which required digitalis therapy and history of treatment for syphilis).

|| Includes a 6 year old boy with several lacerations treated by surgical exploration and boric acid compresses, and a 26 year old man with a laceration treated by incision and hot compresses.

lesions was not an immediate need. Under all circumstances, treatment of accessible wounds was instituted only after the patient had received adequate sedative and antitoxin treatment. This principle of management was accepted because it was learned that such disturbance in highly excitable patients could incite potentially fatal asphyxial spasms.¹

The observations made in this investigation confirm the conclusions reached in my study¹ at the University Hospitals, Iowa City, namely, that the principles of surgery to be followed in the treatment of tetanus are identical with those to be recommended in the absence of this disease. The management of wounds must be adapted to the special requirements of each individual case. Under no circumstances is one justified in

resorting to amputation, excision of a local lesion or drainage of a purulent collection for the sole purpose of removing the focus at which toxin is being elaborated. Abel and Hampil¹⁶ have cited evidence which indicates that such procedures do not influence the course of tetanus either in human beings or in animals after the disease has developed. Likewise, McClintock and Hutchings,¹⁷ on the basis of critical animal experiments, concluded that amputation of an affected member at the first appearance of active symptoms of tetanus in no way altered the progress of the disease. The animals given surgical care died in the same time and with the same symptoms as those not surgically treated.

After the injection of appropriate amounts of specific serum, one may rely on circulating antitoxin to neutralize any toxin which may continue to be discharged from the point of infection. In the presence of a persistent focus of infection, the possibility of recurrences cannot be denied. For this reason, after acute signs and symptoms have been adequately treated, a gentle but careful search for foreign bodies is justified. Even though wounds appear healed, splinters or other extraneous material may be discovered by careful surgical exploration. However, if nail puncture wounds appear to be healed, surgical exploration does not seem necessary. In the presence of purulent collections, debridement, drainage and removal of any foreign bodies from all wounds are necessary. Irrigation with hydrogen peroxide, dilute solution of sodium hypochlorite (Dakin's solution), solution of potassium permanganate or some other oxidizing solution may aid in establishing free drainage and local repair. However, such procedures do not seem to affect the natural course of the tetanus intoxication.¹⁸ Although amputations and other disfiguring operations are to be avoided as far as is feasible, if a structure is already hopelessly destroyed surgical removal is indicated. Gas gangrene must be treated as a special complication. It is perhaps timely to mention that injuries caused by aerial attacks on civilian or military populations will require the most skilful types of surgical management.

GENERAL MANAGEMENT

As soon as tetanus was recognized, the patient was placed under the care of a specially organized tetanus team which consisted of a group of nurses and resident physicians who were instructed regularly concerning all the details of routine treatment. During the earlier part of the study

16. Abel, J. J., and Hampil, B.: Researches on Tetanus: IV. Some Historical Notes on Tetanus and Commentaries Thereon, *Bull. Johns Hopkins Hosp.* **58**:343-376 (Dec.) 1935.

17. McClintock, C. T., and Hutchings, W. H.: The Treatment of Tetanus, *J. Infect. Dis.* **13**:309-320 (Sept.) 1913.

18. Coleman, G. E.: Experimental Study of Tetanus, *J. Infect. Dis.* **47**:410-415 (Nov.) 1930.

(after July 1933) the patients were treated in their respective wards, later, in order to effect a greater degree of centralization, they were transferred to a special ward in the hospital. An adequate supply of printed instructions was available to guide the members of the hospital staff.

The general management of these patients was the same as that for the series treated at the University Hospitals¹ in Iowa City, and may be outlined as follows:

1. *Special Nursing Care.*—Special attendants may be released when the patient is able to walk or move around the sickroom in an invalid chair. In the absence of constant nursing care, patients may succumb to hypostatic pneumonia, dehydration, starvation, physical injuries or sudden fatal asphyxia. No patient who has had convulsions should be placed in a general ward until the danger of a delayed serum reaction, with a possible recurrence of convulsions, has passed (see section on "Serum Therapy").

2. *Maintenance of an Adequate Fluid and Caloric Intake.*—This requirement must be met with but minimal disturbance to the patient. It is much more important to keep the patient quiet than to meet theoretic metabolic needs. A diet high in carbohydrate is desirable. Attempts at feeding by any route should be abandoned immediately if they incite asphyxial convulsions. If the sedatives relieve the swallowing difficulty (trismus and pharyngeal spasms), a liquid or soft diet may be given orally. The food is to be offered at the onset of relaxation, and the patient is never to be awakened for feedings. Liquids should be fed literally drop by drop, by means of medicine droppers with attached rubber tubing. Some patients fare better with glass suction tubes, whereas others drink more easily with the ordinary infant's nursing bottle and nipple. In the presence of intractable difficulty in swallowing one may employ daily intravenous injections of 1,000 to 2,000 cc. of a 5 per cent solution of dextrose in Hartmann's buffered solution. If necessary, veins should be exposed at the ankle or the cubital fossa, with the region under local anesthesia. Except for the occasional convalescent patient with a markedly swollen tongue, nasal feedings should be avoided because of the danger of inciting asphyxial spasms. Transition to the regular diet should be gradual. Repeated transfusions from suitable donors may be of value in combating the associated inanition and possibly in assisting the immunologic defense mechanism.¹⁹

3. *Treatment of Constipation and Retention of Urine.*—These disturbances may be caused by hypertonicity of the sphincters and may incite acute abdominal discomfort, at times colicky and difficult of differentiation from the pain associated with tetanic contractions of the abdominal wall. If the pain is of gastrointestinal origin, relief may be obtained by the use of cleansing enemas and of atropine sulfate administered by mouth or by hypodermic injection. To prevent such difficulties, enemas may be required every other day. If distention of the urinary bladder occurs,²⁰ catheterization, followed by the instillation of a 1:5,000 solution

19. Seven patients (4 recovered and 3 died) received blood transfusions.

20. Retention of urine was recorded for 7 patients of the old series and for 11 of the new. Nine of these patients were children (3 to 14 years old) and the remainder were adults (26 to 59 years old). Seven patients (3 children) of the new series were catheterized on at least one occasion. Of those with urinary retention, death occurred in 5 patients of the old series and 2 of the new.

of potassium permanganate or some other appropriate antiseptic solution, is indicated.

4. *Measures to Prevent the Occurrence of Pneumonia.*—Procedures adapted to this purpose are as important as serum and sedative therapy. Prolonged rigidity of the thorax, with associated impairment of pulmonary ventilation, may be combated with adequate sedation supplemented by inhalations of 5 to 10 per cent carbon dioxide in oxygen. The inhalations are conveniently given for periods of ten to fifteen minutes at four hour intervals (or oftener if not too disturbing to the patient), but should be withheld if undue excitement is occasioned. A dorsal position should be avoided as far as is feasible by placing the patient on the abdomen or side as much as possible. Frequent tepid sponge baths, protection from drafts and moderate bed clothing reduce the danger of the pneumonia which

TABLE 11.—*Pertinent Data Concerning Thirty-Five Patients with Tetanus Complicated by Pneumonia*

	Old Series	New Series	Total
Number of patients with tetanus.....	180	96	276
Number of patients with pneumonia *.....	9 (5.0%)	26 (27.1%)	35 (12.7%)
Deaths among patients with pneumonia.....	8 (88.8%)	22 (84.6%)	30 (85.7%)
Day of disease pneumonia first observed:			
1st to 7th.....	4	20	24
After 7th	4	4	8
Unknown	1	2	3
Day of hospitalization pneumonia first observed:			
1st to 7th.....	9	24	33
After 7th	1	1
Unknown	1	1
Age of patients in years:			
15 or less.....	4	13	17
16 to 30.....	..	5	5
31 to 50.....	3	6	9
Over 50	2	2	4
Severity of the clinical picture of tetanus:			
Moderate	2	1†	3
Severe	7†	25†	32

* The following diagnostic criteria were employed: (a) clinical appearance in the absence of definite signs in the chest in 6 patients of the old series and in 14 of those in the new (in the latter group, the diagnosis for 3 of 4 of those who died was confirmed by necropsy and for 1 by roentgen examination during life; all showed bronchopneumonia) and (b) clinical appearance confirmed by typical physical signs in the chest in 3 patients of the old series and in 12 of those in the new.

† One patient recovered.

‡ Three patients recovered.

might otherwise follow excessive perspiration and chilling of the general body surface. To relieve the respiratory difficulty occasioned by collections of saliva or other secretions in the nasopharynx, ordinarily it is sufficient to wipe the patient's lips after he has been induced to blow out this material with the head or the whole body turned to one side. At times, mechanical suction, with minimal disturbance to the patient, is required. Elevation of the foot of the bed may possibly aid in directing secretions away from the lower part of the respiratory tract. Atropine sulfate is of little value as a means of preventing pulmonary complications. In fact, the secretions become thick and difficult to expectorate if this drug is employed.

Table 11 reveals that pneumonia was diagnosed for approximately one eighth of all the patients and that the apparent incidence in the new series was approximately five times that observed in the old. Because

of the short duration of life among the fatal cases of the old series and the limited number of necropsies, table 11 does not represent an exact comparison of the two series of patients in terms of this complication. In all likelihood, the incidence of pneumonia was much higher in the old series than the figures would indicate. It is of interest that in all except 2 instances the pneumonia occurred during the first week of hospitalization. The high incidence among children is of significance from the standpoint both of diagnosis and of treatment. Practically all those in whom pneumonia developed had severe forms of tetanus, and pulmonary involvement was not encountered among those with mild forms of the disease.

TABLE 12.—*An Analysis of the Clinical Outcome for One Hundred and Seventy-Seven Patients with Tetanus and Elevated Temperature*

Apparent Cause of Fever	New Series		Old Series		Total	
	Recovery	Death *	Recovery	Death *	Recovery	Death
Pneumonia.....	4	22†	1	8	5	30
Serum therapy.....	4‡	..	26 (25)§	2	30	2
Local lesion.....	2	2	..
Preterminal.....	16 (10)	..	16
Unknown.....	7#	9	11 (9)	65 (47)	18	74
Total.....	17	31	38	91	55	122

* Among those patients who died, the hospital records of 3 in the new series and of 26 in the old series, did not contain information in respect to body temperature.

† Two of these patients had septic parotitis (1 with an associated septic abortion), and a third (a 59 year old man) had marked stomatitis and signs of extreme physical neglect.

‡ In 3 of these patients the fever was associated with late serum sickness, and in 1 it was associated with an acute thermal reaction to an intravenous injection of 60,000 units of tetanus antitoxin (temperature, 104 F.). In the latter patient stomatitis prolonged the febrile period.

§ The figure in parentheses indicates the number of patients who received intrathecal serotherapy. One of the 25 patients here indicated had an acute serum reaction (temperature 105.4 F.) about fourteen hours after the intramuscular, intravenous and intraspinal injection of 50,000 units of antitoxin. A more protracted fever was apparently caused by a septic abortion present at the time of hospitalization.

Two of these patients had received sulfapyridine orally on the first appearance of fever.

The high mortality rates recorded in table 11 reflect the ominous outlook of the pneumonia which occurred as a complication of tetanus in the era which preceded the introduction of specific chemotherapy and serotherapy. Although sulfapyridine (2-[paraaminobenzenesulfon-amido]-pyridine) was used in the treatment of but 2 patients with pneumonia²¹ and type-specific serum in the treatment of only 1,²¹ it

21. A 6 year old boy died on the fifth day of his stay in the hospital despite the intravenous injection of 105 grains (6.89 Gm.) of sodium sulfapyridine during a period of about three days and of 145,000 units of type-specific (type not recorded on chart) antipneumococcus serum, given as four doses in two days. Recovery occurred in the case of an 8 year old girl with severe tetanus who received 100 grains (6.5 Gm.) of sodium sulfapyridine intravenously in approximately three days. The response to chemotherapy was spectacular. The patient appeared

would not seem illogical to anticipate that the early institution of chemotherapy and serotherapy²² might reduce the fatality rate among patients with tetanus in whom pneumonic complications develop. In the presence of elevations in temperature of unexplained origin (table 12), the existence of pneumonia is to be suspected, and sulfapyridine should be administered even before typical pulmonary signs appear.²³ As noted in a footnote to table 12, such a policy was adopted in the care of 2 of the patients who recovered. Although this study does not warrant the presentation of any conclusions concerning the therapeutic value of oxygen²⁴ and the other measures employed in the treatment of pneumonia, it seems reasonable to propose that the pneumonia which occurs in a patient with tetanus should receive essentially the same type of management as that which occurs under other circumstances.

RESULTS

Table 13 reveals four important facts. 1. The percentage incidence of mild tetanus was approximately the same in the old and in the new series (17.8 and 21.9 per cent, respectively), that of moderately severe tetanus in the new series was almost twice that in the old (33.3 and 18.8 per cent) and that of severe forms of the disease was about 20 per cent greater in the old series than in the new (63.3 and 44.8 per cent). One can merely speculate concerning the specific roles played by the different types of treatment in determining these relative degrees of severity of the disease. In all probability, however, the omission of intraspinal serotherapy contributed to this reduction in the incidence of severe forms of tetanus. 2. Although the mortality rates among patients with incubation periods of over ten days was about 18 per cent lower than among

to be in a terminal condition at the start of treatment, with rapid, grunting respirations accompanied by cyanosis. The temperature dropped from 104 to 100.5 F. in less than twenty-four hours, and the patient's illness pursued an essentially afebrile course thereafter.

22. Special precautions must be observed to avoid acute anaphylactic reactions because the patient usually has already received antitoxin containing horse serum. If the patient fails to respond to chemotherapy within twenty-four hours, treatment with homologous antipneumococcus serum should be contemplated.

23. Although fever and accelerated respirations should suggest a diagnosis of pneumonia, atelectasis and acidosis must be ruled out by the use of the necessary procedures.¹ Ketone bodies were detected in voided specimens of urine from 5 patients (1 of whom died). A sixth patient (who died) had a marked odor of acetone on the breath, but had no recorded specimen of urine subjected to laboratory examination.

24. The fact that oxygen therapy was employed with variable degrees of thoroughness in this study precludes the presentation of any conclusions concerning the value of such treatment of the pneumonia which may occur as a complication of tetanus.

those with the shorter intervals, it is significant that mortality rates of 42 per cent in the old series and 24 per cent in the new were encountered among the patients with incubation periods of eleven or more days.²⁵ It is obvious, therefore, that a short incubation period justifies a more

TABLE 13.—*An Analysis of the Outcome for Two Hundred and Seventy-Six Patients with Tetanus, with Reference to Incubation Period and Duration of Symptoms Up to the Time of Hospitalization*

Duration of Disease *	Severity of Disease	Series	Incubation Period in Days							
			10 or Less		Over 10		Unknown		All Periods	
			Recov- ery	Death	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death
Four days or less	Mild	Old	9	..	10	..	5	..	24	..
		New	4	..	7	..	2	..	13	..
	Moderate	Old	2	1	6	..	4	1	12	2
		New	14	1 (1)†	6 (1)	..	1	1 ‡	21	2
	Severe	Old	1	61 (3)	1 (1)	24 (1)	..	12 (1)	2	97
		New	7 (1)	21 (11)§	2 (1)	6 (5)	2 (1)	3 (3)	11	30
	Total	Old	12	62	17	24	9	13	38	99
		New	25	22	15	6	5	4	45	32
Five or more days	Mild	Old	3	..	2	..	3	..	8	..
		New	3	..	4	..	1	..	8	..
	Moderate	Old	4	2	3	1 (1)	6	2 (1)	13	5
		New	3	..	3	..	3	..	9	..
	Severe	Old	2	1	..	4	1	..	3	5
		New	1 (1)	1
	Total	Old	9	3	5	5	10	2	24	10
		New	6	..	7	1	4	..	17	1
Not stated	Moderate	Old	1	1	1	1
		New
	Severe	Old	..	2	..	1 (1)	..	4	..	7
		New	1 (1)	..	1
	Total	Old	1	2	..	1	..	5	1	8
		New	1	..	1
All patients	Mild	Old	12	..	12	..	8	..	32	..
		New	7	..	11	..	3	..	21	..
	Moderate	Old	7	3	9	1	10	4	26	8
		New	17	1	9	..	4	1	30	2
	Severe	Old	3	64	1	29	1	16	5	109
		New	7	21	2	7	2	4	11	32
	Total	Old	22	67	22	30	19	20	63	117
		New	31	22	22	7	9	5	62	34

* Antitoxin was administered on the day of hospitalization, except as follows: (a) a delay of twenty-four hours or less for 5 patients of the old series and (b) omission of serotherapy for 2 patients of the new series (mild disease) and for 11 of the patients of the old series (early death).

† The number in parentheses indicates the incidence of pneumonia.

‡ One patient had a remarkable irregular heart which failed to respond to treatment with digitalis.

§ Of those with pneumonia, 2 had septic parotitis (1 with an associated septal abortion), and 1 had marked stomatitis and evidences of neglect (59 year old man). A patient without pneumonia had nonprotein nitrogen retention.

25.	Incubation Period in Days									
	2 to 5	6 to 10	11 to 15	16 to 20	21 to 30	34 to 85	Unknown	All Periods		
Old series	32 (29)*	57 (38)	31 (15)	8 (5)	9 (7)	4 (3)†	39 (20)	180 (117)		
New series	14 (7)	39 (15)	17 (5)	5 (1)	7 (1)	—	14 (5)	96 (34)		

* The figures in parentheses indicate the number of deaths.

† The 3 patients who died had incubation periods of thirty-four, thirty-eight and fifty-six days, respectively.

serious prognosis than does one of greater duration. Nevertheless, it is apparent that for the individual patient with tetanus the incubation period is of limited prognostic value. 3. In both series the vast majority of the deaths occurred among those patients who sought medical care during the first four days of the disease (84.6 per cent in the old series and 94 per cent in the new). These figures reflect the greater incidence of severe tetanus among those hospitalized early than among the group admitted after the fourth day of the disease. For example, approximately 65 per cent of all patients admitted early, in contrast to about 17 per cent of those hospitalized later, had severe forms of tetanus. It is significant that essentially the same percentage of patients in the two series was admitted during the first four days of the disease, and it is noteworthy that the incidence of severe forms of tetanus among those hospitalized early was 19 per cent lower in the new series than in the old (53.2 and 72.2 per cent, respectively). In this respect it is to be restated that this lower incidence of severe tetanus represents a difference probably attributable to the omission of meddlesome types of serum treatment. On the other hand, it is important to emphasize that among those patients admitted during the first four days of the disease potentially fatal complications were recognized much more frequently in the new series than in the old. Thus, the diagnosis of pneumonia was made for 24 of 77 patients of the new series and only 6 of 137 patients of the old series. Likewise, if the two series are compared without considering the time of hospitalization, this apparently higher incidence of pneumonia in the new series becomes even more pronounced (table 11). The diagnosis of other potentially fatal associated conditions among patients of the new series is described in a footnote to table 13. 4. Approximately 94 per cent of the 151 deaths occurred among the 157 patients who had severe forms of tetanus and 84 per cent among the severely ill patients hospitalized during the first four days of the disease. If all patients with severe tetanus are considered, a difference of 21 per cent in the mortality rates suggests a superiority of the new method of treatment. This difference becomes 25 per cent if the comparison is confined to a consideration of the patients with severe tetanus who were hospitalized during the first four days of the disease. If the patients with moderate and severe forms of tetanus are considered in a single group,²⁶ the new series shows a mortality rate (45.3 per cent) which is approximately 34 per cent lower than that calculated for the old series (79 per cent). These results,

26. The patients with moderate and severe tetanus are best considered as a single group because the distinction was at times arbitrary and frequently difficult. Furthermore, it appears likely that many of the patients with severe tetanus in the old series would have presented moderately severe clinical pictures if intraspinal therapy had been omitted and effective sedative and general therapy had been employed.

apparently indicating the superiority of the later methods of treatment, are reflected in gross mortality rates which are approximately 30 per cent lower in the new series (35.4 per cent) than in the old (65 per cent).

Study of table 14, which records the general trend of the mortality rates from 1908 to July 1940,²⁷ discloses five important points. 1. The

TABLE 14.—*The Mortality Among Patients with Tetanus at Cook County Hospital**

Period	Intensity of Disease						All Intensities		
	Mild		Moderate		Severe		All Intensities		Mortality Percentage
	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death	Recov- ery	Death	
1908-1913 (Irons, E. E.: J. A. M. A. 44: 1552-1554 [May 8] 1915).....	12	41	77.3
1914 (Irons, E. E.: J. A. M. A. 44: 1552-1554 [May 8] 1915).....	6	8	57.1
1917-1921 (Calvin, J. K., and Goldberg, A. H.: J. A. M. A. 94: 1977-1981 [June 21] 1930).....	19	25	56.4
1922.....	6	..	3	2	2	7	11	9	45.0
1925.....	5	..	3	2	..	16(1)†	8	18	69.2
1926.....	1	2(2)	1(1)	5	2	7	77.7
1927.....	2	..	1	9	3	9	75.0
1928.....	4	..	1	1	1	19(1)	5	20	80.0
1929.....	1	..	3	9(2)	4	9	69.2
1930.....	3	..	1	1	1	10(1)	5	11	68.7
1931.....	3	19	3	19	86.4
1932.....	2	..	5	4(1)	7	4	36.3
1933 (to July).....	2	..	3	5	5	5	50.0
1933 (after July).....	2	..	1	2(2)	3	2	40.0
1934 †.....	1	..	6	1(1)	2	4(3)	9	5	35.7
1935 §.....	3	..	2	6(3)**	5	6	54.5§
1936 †.....	2	..	2	..	5	9(5)	9	9	50.0
1937.....	4	..	3	..	2(1)	2(2)	9	2	18.2
1938.....	5	..	3(1)	1††	1(1)††	5(4)§§	9	6	40.0***
1939.....	3	..	7	..	1(1)†††	4(2)†††	11	4	26.6
1940 (to July).....	1	..	6	7	..	0

* The records of patients admitted in 1921 and thereafter have been analyzed in detail and have been considered in table 13 (and the other tables in this report) under the designation "old series."

† The figures in parentheses indicate the number of patients with pneumonia at some time during their stay in the hospital.

‡ A total of 3 patients was treated during 1934 and 1936 with definite departures from the new routine (overzealous sedative therapy, in particular).

§ The tetanus team was not as effectively organized during this period as in preceding and subsequent years. The patients were not centralized, and sedative therapy was unusually intensive in 1935.

** A 41 year old man had retention of nonprotein nitrogen (53.3 mg. urea nitrogen and 3.3 mg. creatinine per hundred cubic centimeters of blood).

†† A 60 year old man had a markedly irregular heart.

††† A 13 year old Negro boy whose pneumonia (upper lobe of left lung) resolved spontaneously and by crisis.

§§ Of those with pneumonia, 1 patient (a 19 year old woman) had septic parotitis and a septic abortion and another (a 59 year old man) had severe stomatitis and other evidences of extreme marked physical neglect preceding hospitalization.

*** If the 3 deaths associated with complications other than pneumonia are excluded, the corrected mortality rate for 1938 is 25 per cent.

†††† An 8 year old girl who showed a dramatic response to intravenous injections of sodium sulfapyridine.

††††† A 6 year old boy had pneumonia and septic parotitis. Neither condition responded to treatment with intravenous injections of sodium sulfapyridine or type-specific antipneumococcus serum.

27. As noted in table 14, the data could not be obtained from the record room for the years 1915, 1916, 1923 and 1924.

gross mortality rate for the period of seven years after July 1933 was 32 per cent lower than that for the preceding period of approximately twenty years, in which the older methods of management were employed. 2. With the former types of treatment, the general trend of the mortality was between 50 and 86.4 per cent. The years 1922 and 1932, however, show unusually low mortality rates. Although the mortality showed marked yearly fluctuations after July 1933, the absence of the exceedingly high peaks previously encountered is significant. Likewise, the unusually low death rates in 1934, 1937, 1939 and 1940 are worthy of attention. Although the results for 1935 appear to be poor, it is to be emphasized that the new routine was not strictly followed during this limited period. The rise in the mortality rate in 1938 was caused by the inclusion of 3 patients who presented conditions which in them-

TABLE 15.—*The Relation of the Site of Injury to Mortality*

Site of Lesion	Series	Number of Patients	Percentage of Patients of Series *	Number of Deaths	Per Cent Mortality
Upper extremity.....	Old	70	38.9	48	68.5
	New	20	20.8	6	30.0
Lower extremity.....	Old	74	41.1	51	68.9
	New	48	50.0	17	35.4
Head and neck.....	Old	7	3.9	3	42.8
	New	12	12.5	4	33.3
Trunk and external genital organs...	Old	3	1.7	2	66.6
	New
Interior of abdomen.....	Old	3	1.7	2	66.6
	New	2	2.1	1	50.0
Unknown or indeterminate.....	Old	23	12.7	11	47.8
	New	14	14.5	6	42.8
All sites.....	Old	180	100.0	117	65.0
	New	96	99.9	34	35.4

* The number of patients is divided by the number of patients in the series.

selves could have caused death. As noted in a footnote to table 14, omission of these 3 patients yields a corrected mortality rate of 25 per cent for 1938. 3. The main reduction in mortality was among those patients with moderately severe forms of tetanus. 4. The yearly mortality rate for those with severe tetanus reached the lowest level in 1937, when 2 of 4 patients recovered. Otherwise, the fatality rate among those with severe tetanus varied from 64.3 per cent in 1936 to 80 per cent in 1939. 5. The presence of pneumonia and of other complications in the new series influenced the mortality rates in a definite manner. The importance of the proper treatment of these complications has already been discussed in the section on "General Management."

A comparison of the two series of patients in terms of the severity and the site of the local lesion indicated that neither of these factors bore any significant or consistent relation to the mortality rates (tables 9 and 15). The observations recorded in table 15, as well as those reported

elsewhere,²⁸ are at variance with the belief that the closer the local focus to the central nervous system the greater is the death rate. In this respect, it is of interest that the lowest mortality was encountered among those patients who presented lesions in the region of the head and neck.

The patient's age must be considered in the prognosis. It has been reported¹ that the mortality from tetanus is highest at the extremes of life. For this reason, it is significant that the old and the new series were essentially similar in respect to the percentage distribution of the patients in terms of age group. It is of interest that in the old series the mortality rate was high in all age periods, with the lowest figure among patients 16 to 30 years old and the highest among those over 50 years of age. On the other hand, analysis of the new series revealed no consistent relation between the age of the patient and the mortality rate.

TABLE 16.—*The Relation of Age to Mortality*

Age Period in Years	Series	Number of Patients	Percentage of Patients *	Number of Deaths	Percentage of Deaths *	Per Cent Mortality
1 to 15.....	Old	88	48.9	53	45.3	60.2
	New	41	42.7	13	38.2	31.8
16 to 30.....	Old	35	19.4	17	14.5	48.6
	New	17	17.7	8	23.5	47.0
31 to 50.....	Old	41	22.8	32	27.4	78.0
	New	28	29.2	7	20.6	25.0
51 to 78.....	Old	16	8.9	15	12.8	93.7
	New	10	10.4	6	17.6	60.0
All age periods.....	Old	180	100.0	117	100.0	65.0
	New	96	100.0	34	99.9	35.4

* The number of patients or the number of deaths is divided by the number of patients in the series.

Nevertheless, it is significant that the highest mortality rate in the new series was noted among the members of the oldest age group.

The temperature of patients with uncomplicated tetanus is usually normal.¹ As indicated in table 12, 177 patients had a record of fever at some time during their stay in the hospital. Approximately 69 per cent of these 177 patients died. In contrast, no deaths occurred (new series) among those whose record indicated a normal temperature (table 12). Tables 11 and 12 describe the importance of pneumonia as a cause of fever, particularly in the new series. Serum therapy was a more important cause of pyrexia in the old series than in the new. This is explained by the fact that repeated injections of tetanus antitoxin (usually intraspinal) were given to patients of the old series. Because of the varied etiologic relations of the fever and because reasons for pyrexia were unknown in one third of the patients of the new series and in approxi-

mately two thirds of those in the old, it seems unnecessary to compare the two groups of patients in terms of the incidence of elevated temperature.

SUMMARY AND CONCLUSIONS

From 1921 to July 1933 patients with tetanus admitted to the Cook County Hospital had been given general ward care, a variety of sedatives and tetanus antitoxin by various technics. About 80 per cent had received serum by the intrathecal route alone or in combination with other channels. In general, repeated doses were injected, so that the averages were approximately 102,000 units for 63 patients who recovered and 58,000 units for 106 who died. In respect to the local lesions, about one half of the entire group of patients had received no treatment, about one-fourth had surgical care and the rest had nonsurgical care. Since July 1933 a new routine has been followed. This has consisted of systematic sedation with avertin with amylene hydrate and sodium amytal (either of the drugs alone or the two in combination), single intravenous and/or intramuscular injections of antitoxin in doses ranging from 20,000 to 100,000 units, the avoidance of any particular emphasis on care of the local lesions and careful general management, with stress on constant nursing care, measures to prevent pneumonia and maintenance of an adequate fluid and caloric intake. One hundred and eighty patients have been treated by the old routine and 96 by the new method.

Comparison of the two series of patients indicates that the incidence of severe forms of tetanus in the old series was about 20 per cent higher than that in the new. The presence of complications, particularly pneumonia, was recognized much more frequently in the new series than in the old.

Approximately 94 per cent of all deaths occurred among those with severe forms of tetanus, and 84 per cent among the severely ill patients hospitalized during the first four days of the disease. The gross mortality rate for the new series (35.4 per cent) was approximately 30 per cent lower than that noted for the old (65 per cent). A significant difference in the mortality rates was demonstrable even when the data were subjected to more rigid methods of statistical analysis. The yearly mortality rates have shown marked fluctuations from 1908 to July 1940, with a well marked tendency toward significantly lower peaks since July 1933. The main reduction in mortality has been among those with moderately severe tetanus. Coexisting diseases and complications influenced the yearly mortality rates.

In uncomplicated tetanus, ordinarily the temperature is normal. About 69 per cent of the patients with fever died, whereas no deaths occurred among those whose temperature remained normal. The cause of the fever was of prognostic significance, as was revealed by the ominous import of pulmonary involvement.

Sedative therapy is the keystone of treatment, and all patients should receive proper sedation. Sodium amytal and avertin with amylene hydrate have proved to be superior to the sedatives previously employed, but the ideal depressant remains to be discovered.

From both the theoretic and the practical point of view, intrathecal serum treatment is to be condemned. Both intraspinal and intracisternal serotherapy are disturbances which apparently increase the intensity of neuromuscular irritability in tetanus.

The intravenous and intramuscular routes, preferably the intramuscular, are recommended for routine use. The technic advised for the administration of antitoxin has been described.

Titration and clinical studies indicate that a single dose of 30,000 units of tetanus antitoxin is satisfactory for active treatment. To allow a liberal margin of safety, a dose of 60,000 units is arbitrarily advised for patients admitted for treatment during the first five days of the disease and one of 40,000 units for mildly to moderately ill patients first treated after the fifth day of disease.

For patients with active tetanus, care of the local lesions is ordinarily not an emergency need and appears to be of relatively minor importance. Amputations and similar measures are warranted only when structures appear to be irreparably destroyed. Treatment of wounds with oxidizing or other solutions may facilitate drainage and may aid the process of healing, but it cannot destroy the tetanus bacilli present locally. The principles of treatment to be followed in the care of wounds in patients with tetanus are identical with those to be recommended in the absence of this disease.

The prompt treatment of complicating pneumonia by present day methods of chemotherapy and serotherapy, in conjunction with customary routine measures, is indicated when this complication supervenes in patients with tetanus.

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BIOLOGIC FALSE POSITIVE SEROLOGIC REACTIONS IN TESTS FOR SYPHILIS

II. OCCURRENCE WITH ORGANIC DISEASES OTHER THAN SYPHILIS

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Many infectious diseases have been reported as causing biologic false positive serologic reactions for syphilis. That some of them (malaria, leprosy and infectious mononucleosis) cause such reactions has been well established. Other diseases, e. g., relapsing fever, rat bite fever, scarlet fever, tuberculosis, pneumonia, Vincent's infections, malignant conditions (particularly cancer of the tongue), subacute bacterial endocarditis, glanders, Weil's disease, leishmaniasis, lymphogranuloma venereum, trypanosomiasis, typhus fever, vaccinia and infections of the upper respiratory tract, as well as injections of horse serum, have from time to time been suggested as causing such serologic reactions, but the evidence is as yet inconclusive.

From a review of the literature it is impossible to arrive at any conclusions regarding the percentage of biologic false positive reactions obtained in any of these diseases except leprosy and infectious mononucleosis. Until recently it was thought that biologic false positive reactions were obtained in only 10 to 15 per cent of patients with malaria. When this disease was carefully studied by means of serially repeated tests, first by Ester¹ and later by Kitchen, Webb and Kupper,² it was found by them that 90 to 100 per cent of malarial patients at some time in the course of the disease had biologic false positive serologic reactions for syphilis. These observations strongly suggest that, particularly in infectious diseases, the incidence of false positive reactions cannot be

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1. Ester, F.: Sul comportamento di alcune sieroreazione della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, *Gior. di batteriol. e immunol.* **17**:502 (Oct.) 1936.

2. Kitchen, S. F.; Webb, E. L., and Kupper, W. H.: The Influence of Malarial Infection on the Wassermann and Kahn Reactions, *J. A. M. A.* **112**:1443 (April 15) 1939.

determined by single specimens of serum. Serial specimens, taken daily if possible, should be studied, as the false positive reactions may occur on only one or two days.

To illustrate the type of serologic response associated with infectious diseases, we have selected for report 11 cases in which biologic false positive serologic reactions for syphilis were associated with infections other than syphilis.

REPORT OF CASES

CASE 1.—A white man aged 26, a physician, had a serologic test for syphilis in November 1938, because he wished to act as a donor for a transfusion. The result of this test was reported as positive. Reactions in serologic tests for syphilis performed on several occasions during the two years prior to this test had always been negative. There was no history of sexual exposure or of accidental infection with *Spirochaeta pallida*. About one week after the positive reaction was reported, low grade fever developed, with a daily temperature ranging from 99 to 99.8 F. There were no symptoms other than malaise, fatigue and, at times, excessive perspiration. Physical examination disclosed nothing abnormal except one palpable left posterior auricular node, a few shotty nodes in the posterior cervical triangles and a few small nodes in the left axilla. The edge of the spleen was definitely palpable. Routine laboratory studies yielded data as follows: The red blood cell count was 4,670,000; the hemoglobin concentration, 91 per cent; the white blood cell count, 7,850, and the differential count, 64 per cent neutrophils, 31 per cent lymphocytes, 4.5 per cent monocytes, and 0.5 per cent basophils. The red and white blood cells were apparently normal. No malarial parasites were seen in the blood smear. The urine and stool were normal. A test for heterophil antibody gave negative results. The agglutination test for typhoid H was positive in a dilution of 1:160 and doubtful in dilutions to 1:1,250. The agglutination test for typhoid O was negative. Agglutination tests for *Bacillus abortus*, *Salmonella suispestifer* and paratyphoid A and B bacilli were all negative. The cerebrospinal fluid showed no abnormal changes.

In June 1939 the patient married. In spite of the fact that he has received no antisyphilitic treatment and that no prophylactic precautions have been taken in sexual relations, his wife remains free from syphilis (May 1940).

In August 1939, while in another city, the patient had an acute attack of abdominal pain, with boardlike rigidity of the abdomen. His temperature was 99 F. The white blood cell count was 14,500, with 90 per cent neutrophils. It was thought that possibly he had a perforated gastric ulcer or acute pancreatitis. A laparotomy was performed, but nothing could be found except an enlarged spleen. He made an uneventful recovery and has had no recurrence of the abdominal pain. Unfortunately, no serologic test for syphilis was done during this episode.

In January 1940 he was reexamined; he was asymptomatic, and nothing abnormal was found on physical examination. Laboratory studies gave information as follows: The red blood cell count was 4,820,000, and the white blood cell count, 9,400 with a normal differential count. The agglutination test for typhoid H was reported as weakly positive in a dilution of 1:80. The agglutination test for typhoid O was negative. The serologic tests for syphilis are summarized in table 1.

The exact nature of this patient's infection is unknown. In November 1938, several weeks after the onset of his first illness, he was still suffer-

ing from malaise and fatigue and had a palpable spleen. At that time it was our impression that he might have either infectious mononucleosis or brucellosis, though neither of these diseases could have been responsible for the acute abdominal pain which developed eleven months later. This may have been an entirely different infection, but in view of the fact that the patient still had an enlarged spleen at the time of operation and has persistently had a slight elevation of the white blood cell count, it is reasonable to believe that the two episodes were related and that the patient was suffering from an infection of unknown cause and that this involvement has now subsided. Concurrently, the serologic tests for

TABLE 1.—*Serologic Tests for Syphilis, Case 1**

Date	Lab- ora- tory	Was- ser- mann	Kahn Stan- dard	Eagle Micro- floccu- lation	Eagle Macro- floccu- lation	Kline Diag- nostic	Hin- ton	Laugh- len	Spiro- chetal (Pal- lida)	Clinical Findings
9/37	1	0	Normal
7/38	1	0	
11/ 1/38	2	P	D	D	..	Normal
11/ 3/38	2	P	D	D	..	
11/17/38	2	P	D	Fever, malaise and fatigue, beginning Nov. 6
11/18/38	2	..	0	D	..	
11/22/38	1	0	..	0	Malaise, fatigue, adenopathy and en- larged spleen
11/26/38	3	0	0	..	0	
	4	0	P (1 unit)	0	..	P (3 units)	0	
2/28/39	4	D	D	0	..	P (1 unit)	0	..	0	Good health, except for acute abdominal pain Aug. 24, 1939
3/15/39	3	0	0	..	0	
8/15/39	4	0	0	0	..	D	0	
1/31/40	3	0	0	..	0	0	

* In this table and in subsequent tables, laboratories are designated as 1, 2, 3, etc. Results of serologic tests are expressed as positive (P), doubtful (D), negative (0) and anti-complementary (A. C.). If a quantitative titration in a positive test was performed, the titer, expressed in units of reagin (serum dilution), is parenthetically inserted after the positive result.

syphilis, which gave only weakly positive reactions and which were marked by conflicting results from different laboratories and with different technics, have spontaneously given negative reactions and have continued to do so for nearly a year.

CASE 2.—A white man aged 24, a physician, acted as a blood donor on numerous occasions during the four years he was in medical school. Results of serologic tests for syphilis, done before each transfusion, were always negative. He was examined here on Oct. 27, 1938. Five weeks prior to this examination he had had a head cold and slight cough, which were followed in a few days by an abrupt onset of deafness and tinnitus in the left ear. Within twenty-four hours after the onset of these symptoms, vertigo developed, with nausea and nystagmus. The temperature at the onset of this illness was 98.6 F. Three weeks after the onset of symptoms, serologic reactions for syphilis were found to be positive. There was no history of either acquired or congenital syphilitic infection. The physical

examination showed no abnormal condition except in the ears. Complete audiographic studies were made. There was marked bilateral loss of hearing, more striking on the left side. Air conduction was greater than bone conduction on both sides, and vibration sense in Weber's test was referred to the right. At the time of examination, on October 25, the vertigo had disappeared but the loss of hearing had progressed. Otherwise the patient felt well. The results of routine laboratory studies were without significance. Examination of the cerebrospinal fluid revealed nothing abnormal. On reexamination by the otolaryngologist in June 1939, it was noted that the patient still had tinnitus in the left ear but that hearing in both ears had returned to normal. A summary of the serologic findings is outlined in table 2. No antisyphilitic treatment was given at any time.

Labyrinthitis, of unknown cause, developed in September 1938. Apparently during its course reagin appeared in the patient's blood. The

TABLE 2.—*Serologic Tests for Syphilis, Case 2*

Date	Lab- ora- tory	Was- ser- mann	Kahn Stan- dard	Eagle Micro- floccu- lation	Eagle Macro- floccu- lation	Kline Diag- nostic	Hin- ton	Kline Exclu- sion	Clinical Findings
10/11/38	1	0	P	P	..	P	Slight vertigo and tinnitus; moderate loss of hearing; no fever
	2	0	..	P	
10/21/38	3	..	0	D	..	P	
	3	0	0	..	0	No tinnitus or vertigo; moderate loss of hearing; no fever
10/25/38	1	0	D	0	..	D	..	P	
	2	0	..	0	
10/27/38	3	D	..	P	
	5	..	D	0	P	
	6	0	0	..	0	Well; occasional tinnitus; normal hearing
11/ 4/38	7	0	1 & 1:10 0 0 0	1 & 1:10 0 0 0	..	1 & 1:10 P 0 0	0	..	
	7	0	0	0	..	0	0	..	
4/14/39	7	0	0	0	..	0	0	..	

results of serologic tests for syphilis spontaneously reversed to negative within three weeks and have remained so for six months.

CASE 3.—A white man aged 33, an economist, presented himself to his family physician for a routine physical examination. A serologic test done at the time gave a positive reaction. Two weeks before this examination the patient had been vaccinated against smallpox. Twenty-four hours after vaccination he had a fever lasting one day; the fever returned after several days and then lasted about four days. The temperature was at times as high as 103 F. For the next few weeks the patient felt weak and had frequent gastrointestinal upsets. At the time he was examined by his physician the vaccination scar had not healed. The patient gave no history of primary or secondary syphilis. Four to five years previously he had a sore throat which was diagnosed as Vincent's infection, but this was not associated with symptoms suggesting the early stages of syphilis. The lesion in the throat disappeared in one week with local treatment. One year ago the patient was told that he had an ulcerative lesion of the nasal septum; it lasted about six weeks, in spite of local treatment. About four years ago he had gonococcic urethritis, complicated by epididymitis. The onset of gonorrhea followed

his only extramarital sexual exposure. The patient has been married for six years, and his wife has negative serologic reactions for syphilis. Physical examination showed nothing abnormal except epidermophytosis of the feet, an unhealed vaccination wound (dark field examination of serum expressed from this yielded nothing significant) and slight induration of the right epididymis. All routine laboratory tests, with the exception of the serologic tests for syphilis, revealed nothing significant. An occasional red blood cell was seen in one specimen of urine. The urine was entirely normal on repeated examinations. A test for heterophil antibody gave negative results. The cerebrospinal fluid was normal. The serologic tests are summarized in table 3.

This patient had a marked local and constitutional reaction to small-pox vaccine. Because the reactions to serologic tests for syphilis were positive during the time the vaccination reaction persisted and became

TABLE 3.—*Serologic Tests for Syphilis, Case 3*

Date	Lab- oratory	Wasser- mann	Kahn Standard	Eagle Micro- floccu- lation	Eagle Macro- floccu- lation	Clinical Findings
8/ 1/38	1	P	P	Malaise; vaccination wound from inoculation July 15; no fever
8/13/38	2	P (2.5 units)	P	..	P	Vaccination wound not healed
8/15/38	2	P (2.5 units)	P	..	P	
8/17/38	3	D	P	
8/25/38	2	0	0	..	0	
8/26/38	4	P (4 units)	..	P	..	Vaccination wound healed; well
9/ 7/38	2	0	0	..	P	} Well
9/14/38	2	0	0	..	P	
9/21/38	2	0	0	..	0	
9/23/38	2	0	0	..	0	
11/ 9/38	2	0	0	..	0	

negative shortly after the constitutional and local reaction had subsided, we believe vaccinia to be responsible for these false positive serologic reactions for syphilis. This is the second case reported in the literature in which such a response occurred.

Barnard³ reported the first case in which a biologic false positive serologic reaction for syphilis was caused by vaccinia. The patient was a white student 24 years of age who had had repeatedly negative serologic reactions before he was vaccinated, the last negative response being obtained six months before vaccination. A routine serologic test done during the period when the local vaccination lesion was present gave a positive response. The serologic reactions reverted to negative after

3. Barnard, R. D.: False Positive Serologic Tests for Syphilis Following Vaccination for Variola, Illinois M. J. **77**:78 (Jan.) 1940.

four weeks and remained negative when repeated during the following four months. Giordano ⁴ has observed, but not reported, a similar case.^{4a}

CASE 4.—A white man aged 24, a store manager, was admitted to the hospital on Oct. 23, 1937 with bronchopneumonia. For two weeks prior to his admission he had had fever, the temperature occasionally reaching 102 F. He had been suffering from generalized aches and pains and had had a cough for about one week prior to admission. There was no history of acquired or congenital syphilis. On his admission to the hospital, the physical examination showed nothing abnormal except physical signs of consolidation in the left lung. Roentgenologic examination of the chest at this time revealed infiltration of small areas in the upper and middle lobes of the right lung and the upper lobe of the left lung. The routine laboratory studies yielded data as follows: The white blood cell count was 16,200, and the differential count, 12 per cent juvenile neutrophils, 77 per cent neutrophils, no eosinophils, no basophils, 8 per cent lymphocytes and 3 per cent monocytes. Pneumococci could not be typed from the sputum. The blood culture showed no growth. The urine and stool were normal. The level of blood non-

TABLE 4.—*Serologic Tests for Syphilis, Case 4*

Date	Lab-oratory	Wasser-mann	Kahn Standard	Eagle	Hinton	Kline Diagnostic	Clinical Findings
10/28/37	1	P	..	D	Fever; roentgenographic evidence of bronchopneumonia
11/ 2/37	1	P	..	D	
11/ 7/37	1	0	No fever; resolution
11/10/37	1	0	No fever; convalescence
12/ 5/37	2	..	0	0	
1/12/38	2	..	0	0	Well
2/20/38	2	..	0	0	
3/15/39	3	0	0	0	0	0	

protein nitrogen was 40 mg. per hundred cubic centimeters; the level of blood sugar, 81 mg. per hundred cubic centimeters, and the carbon dioxide-combining power, 60 volumes per cent. The level of chlorides was 90.8 milliequivalents per hundred cubic centimeters. The test for heterophil antibody gave a negative result. The serologic tests for syphilis are summarized in table 4.

CASE 5.—A single white woman aged 25, a nurse, had a chill and pain in the chest and began to cough on May 7, 1938. She was admitted to the hospital two days later and on admission was found to have bronchopneumonia. Pulmonary infiltration was confined to the upper lobe of the right lung. From May 9 to May 15 the temperature ranged from 99 to 102 F. On her admission the white blood cell count was 6,650; the red cell count, 4,890,000, and the hemoglobin concentration, 98 per cent. Pneumococci could not be typed from the sputum; a

4. Giordano, A. S.: Personal communication to the authors.

4a. Since the preparation of this paper false positive serologic reactions for syphilis have been reported in a high proportion of patients with vaccinia by Thomas and Garrity (Routine Kahn Blood Reactions, U. S. Nav. M. Bull. **39**:272 [April] 1941) and by Lynch, Boynton and Kimball (False Positive Serologic Reactions for Syphilis, J. A. M. A. **117**:591 [Aug. 23] 1941).

culture of the sputum contained 20 per cent pneumococci, 20 per cent *Staphylococcus albus* and 60 per cent *Staphylococcus aureus*. Culture of the sputum and guinea pig inoculations of the sputum were negative for tubercle bacilli. Blood cultures showed no growth. On admission, the Eagle flocculation test gave a negative result. Six days after admission, however, the patient was transferred to another ward, where the flocculation test was routinely repeated and the result found to be positive. The patient gave no history of syphilis, nor could any evidence of syphilis be found on physical examination. Results of repeated

TABLE 5.—*Serologic Tests for Syphilis, Case 5*

Date	Lab- oratory	Wasser- mann	Kahn Stan- dard	Eagle Macro- floccu- lation	Eagle Micro- floccu- lation	Hin- ton	Kline Diag- nostic	Spiro- chetel (Pal- lida)	Clinical Findings
5/11/38	1	0	Fever; partial consolida- tion of upper lobe of right lung
5/17/38	1	P	P	Fever; consolidation of upper lobe of right lung
5/28/38	2	P (100 units)	P	P	Convalescence; no fever; no clinical evidence of consolidation
5/31/38	2	P (40 units)	P	P	Discharge from hospital; no fever
6/ 1/38	2	P (40 units)	P	P	Well
6/ 3/38	2	P (13.3 units)	P	P	
6/ 7/38	2	P (13.3 units)	P	P	
6/ 9/38	2	P (13.3 units)	P	P	
6/13/38	3	P (22 units)	P	0	
	2	P (5 units)	P	P	
6/14/38	2	P (1 unit)	P	D	
6/16/38	2	P (1 unit)	P	D	
6/28/38	4	D	P	
7/ 6/38	4	0	
7/12/38	4	D	0	
7/19/38	4	D	0	
7/25/38	4	D	0	
8/23/38	2	0	0	
2/24/39	3	0	0	..	0	0	0	..	
3/ 1/39	1	0	0	
	2	0	0	0	
	3	0	0	..	0	..	0	..	

serologic tests in the five years preceding this admission had all been negative. She admitted sexual exposure with one man only, her fiancé. The man was examined and found to be free from all evidence of syphilis. The patient was afebrile, and the consolidation of the lung had entirely cleared by May 23. A summary of the serologic tests on this patient is given in table 5.

CASE 6.—A white woman aged 40, a housewife, was first admitted to the hospital in 1927, complaining of arthritis of the hands and shoulders. At this time her tonsils and adenoids were removed. No serologic test for syphilis was done. The patient returned to the hospital in 1928, with the new complaints of abdominal pain, nausea, vomiting and diarrhea. She remained in the hospital for only

twenty-four hours, but the routine history and physical examination showed nothing abnormal. Again, no serologic tests for syphilis were done. She was again admitted to the hospital in 1934, because of chronic infectious arthritis of the right thumb. With the exception of the right thumb, which was somewhat swollen and painful on active and passive motion, her physical examination showed nothing abnormal. Results of the serologic tests for syphilis, performed for the first time, were negative.

On Feb. 24, 1935 the patient was again admitted to the hospital, this time because of lobar pneumonia. She had been sick for eight days preceding this admission with what was thought to be grip. The temperature had been ranging from 102 to 103 F. On admission her temperature was 104 F. Physical examination showed signs of lobar pneumonia. Roentgenologic examination of the chest confirmed these findings. Aside from the findings in the chest, the results of the physical examination were entirely normal. She gave no history of syphilitic infection. Type IV pneumococci were found in the sputum. A blood culture yielded no growth. The blood counts were as follows: red cells, 4,120,000; white cells, 20,500, and differential count, 92 per cent neutrophils, no eosinophils, 4 per cent lymphocytes and 4 per cent monocytes. The urine and stool were both

TABLE 6.—*Serologic Tests for Syphilis, Case 6*

Date	Lab-oratory	Wasser-mann	Standard	Eagle Macro-floccu-lation	Eagle Micro-floccu-lation	Kline Diag-nostic	Clinical Findings
6/34	1	0	..	0	Chronic infectious arthritis
2/24/35	1	P	..	P	Fever; lobar pneumonia
2/27/35	1	P	..	P	
1/27/37	1	0	0	..	Well
	2	0	0	0	
12/27/39	1	0	0	Fever; bronchitis; pharyngitis

normal. Routine serologic tests for syphilis were done; the results of the Eagle flocculation test and the Wassermann test were positive. The patient made an uneventful recovery and was discharged.

Although many attempts were made to have her return for serologic examinations, the patient refused to have further tests done until January 1937. Meanwhile, her husband was found to be free from all evidences of syphilis.

The patient was again admitted to the hospital on Dec. 27, 1939, complaining of a head cold and cough of two days' duration. The temperature was 100 F. Nothing could be found on physical examination. The diagnosis was acute bronchitis and pharyngitis. Serologic tests were done at this time, and reactions to the Eagle flocculation and Kline tests were negative. A summary of the serologic tests on the patient is given in table 6.

CASE 7.—A male Negro child aged 15 months was examined in the pediatric clinic on May 23, 1939, when he was found to have marked anemia, bilateral otitis media, rhinopharyngitis and meningismus. There were no lesions or history suggestive of congenital syphilis, and serologic reactions of both the blood and the cerebrospinal fluid were negative for syphilis. The hemoglobin concentration was 30 per cent. The child was admitted to another hospital for treatment. While

at this hospital he received a transfusion because of anemia. The donor for this transfusion had been thoroughly examined and found to be nonsyphilitic. After a lapse of about six weeks, on July 3, 1939, the child returned to the pediatric dispensary with cough and bilateral otitis media still present. Serologic tests for syphilis were repeated and the results reported as positive. Roentgenograms of the long bones were normal, and a roentgenogram of the chest was unsatisfactory.

Physical examination at this time showed nothing significant except otitis media. The child was followed at frequent intervals in the dispensary from July 3 to July 27; during this period his temperature fluctuated between 98.8 and 101.4 F. On July 27 roentgenologic examination of the chest revealed bronchopneumonia of the right lung. The child was admitted to the ward. At this time he was also found to have physical signs of pneumonia of the right lung. His white blood cell count was 27,000, with 89 per cent neutrophils. The hemoglobin concentration on admission was 59 per cent. The child recovered from pneumonia

TABLE 7.—*Serologic Tests for Syphilis, Case 7*

Date	Lab- oratory	Wasser- mann	Eagle Micro- floccu- lation	Kline Diag- nostic	Kline Exclu- sion	Clinical Findings
5/27/39	1	0	Anemia; otitis media; slight fever
7/ 5/39	2	A. C.	P	} Otitis media; slight fever; cough
7/ 7/39	2	A. C.	P	
7/17/39	2	0	D	} Fever; bronchopneumonia
7/25/39	2	0	D	
8/ 2/39	2	0	D	No fever; lungs clearing
9/ 5/39	2	0	D	Fever; nasopharyngitis
11/ 1/39	2	0	0	} Well
1/ 9/40	2	0	0	
2/ 7/40	2	0	0	} Slight fever; cervical adenitis
4/ 3/40	2	0	0	
6/ 5/40	2	..	0	} Well

and was discharged on August 13. He remained well until September 5, when he again had a temperature of 100 F. Nothing could be found to explain the fever except nasopharyngitis. His white blood cell count was 19,400, with 80 per cent neutrophils. The hemoglobin concentration by this time had increased to 82 per cent. The child was well in two days and was discharged. His mother has been examined and gives no history or physical signs of syphilis; her reactions to serologic tests for syphilis are negative. The serologic tests in this case are summarized in table 7.

Unfortunately, serologic tests for syphilis had not been done in case 4 prior to the patient's admission to the hospital with pneumonia. Two or more negative serologic reactions had been obtained in cases 5 and 6 and one in case 7 prior to the patients' admissions with pneumonia. The serologic reactions reverted to negative in all 4 cases after recovery from the acute disease—in case 4 in three days, in case 5 in two months and

in case 7 in one month after the temperature became normal. The interval between recovery from pneumonia and reversion of the serologic reactions for syphilis to negative is unknown in case 6.

Only 1 of these 4 patients had pneumococcic pneumonia; the etiologic agent in the cases of the other 3 patients is not known. None received serum therapy, an important point inasmuch as injections of horse serum have been reported to produce biologic false positive reactions.⁵

Reports of biologic false positive serologic reactions for syphilis associated with pneumonia are few. Eldh⁶ did serologic tests on 20,798 medical patients and found that 52 had presumably biologic false positive reactions. Twenty-six of these 52 patients had pulmonary disease, of whom 10 had pneumonia, 6 emphysema, 7 tuberculosis and 3 influenza with bronchitis. Krag and Lønberg⁷ had a similar experience. In testing the serums of 120,000 presumably nonsyphilitic patients they found that 53 patients had biologic false positive serologic reactions for syphilis, so far as they presented no clinical evidence or history of syphilis infection. Sixty per cent of them⁸ had infections of the respiratory tract, and 13 per cent^{5b} had pneumonia. Boas and Neergaard⁹ reported the cases of 1 patient with bronchopneumonia and 2 with bronchitis whose serums gave biologic false positive reactions. Kissmeyer¹⁰ reported 10 cases, in which the patients had biologic false positive serologic reactions for syphilis. In 2 of these cases the diagnosis of pneu-

5. (a) Hentschel, H., and Szego, L.: Neue Serumbefunde an Diphtherie-Rekonvaleszenten, *Klin. Wchnschr.* **8**:1395 (July 23) 1929. (b) Wichels, P.; Hürthle, R., and Maley: Ein Beitrag zur Theorie und Praxis der Syphilisreaktionen, *München. med. Wchnschr.* **76**:1759 (Oct. 18) 1929. (c) Frei, W.: Serologische Untersuchungen nach Pferdeseruminjektionen, nach Pferdefleisch-sowie nach Ziegenmilchernährung, *Klin. Wchnschr.* **8**:2134 (Nov. 12) 1929. (d) Boas, H., and Tølbøll, G.: Kann eine Injektion von Diphtherieserum eine positive Seroreaktion auf Syphilis bei einem Nicht-Syphilitiker hervorrufen? *Dermat. Wchnschr.* **94**:173 (Jan. 30) 1932. (e) Stern, C.: Positive Seroreaktion auf Syphilis nach Infektion von Diphtherieserum, *München. med. Wchnschr.* **79**:583 (April 8) 1932.

6. Eldh, S. M.: Specificity of the Wassermann Reaction in Almost 21,000 Nonsurgical Cases, *Svenska läk.-tidning.* **29**:373 (April 8) 1932.

7. Krag, P., and Lønberg, A.: The Occurrence of Strong Non-Specific Wassermann-Kahn Reactions, *Acta dermat.-venereol.* **19**:612 (Dec.) 1938.

8. Edelman, S. D., and Haber, G. B.: Rat-Bite Fever: Report of Three Cases with Review of the Literature, *J. Pediat.* **5**:520 (Oct.) 1934.

9. Boas, H., and Neergaard, I. S.: Kommt eine positive Wassermann-Reaktion gelegentlich bei febrilen Lungenaffektionen vor? *Dermat. Ztschr.* **71**:6 (March) 1935.

10. Kissmeyer, A.: Some Views on the Interpretation and Evaluation of the "Nonspecific" Seroreaction in Syphilis, *Ugesk. f. læger* **99**:213 (Feb. 25) 1937.

monia was made. Stryjecki¹¹ stated that about 5 per cent of patients with pneumonia have biologic false positive serologic reactions for syphilis.

CASE 8.—A single white woman aged 19, a nurse, began to complain of malaise, generalized aching and sore throat about March 1, 1935. Twenty-four hours after these first symptoms appeared slight fever developed. About forty-eight hours after the onset of fever a generalized macular eruption appeared over the face and trunk. This rash persisted for about thirty-six hours. The temperature fell to normal when the rash disappeared. The patient said there had been no sexual exposure or recent kissing. No lesions had been present in the past which might suggest an extragenital chancre. The patient had no signs or symptoms of congenital syphilis. The patient's mother and father are living and well. The mother had one miscarriage after the birth of the patient.

TABLE 8.—*Serologic Tests for Syphilis, Case 8*

Date	Lab- oratory	Wasser- mann	Kahn Standard	Eagle Macro- floccu- lation	Eagle Micro- floccu- lation	Kline Diag- nostic	Clinical Findings
3/ 5/35	1	D	P	Fever; macular rash
3/ 7/35	1	P	P	Malaise; fatigue
	2	P	P	
		(16 units)					
3/15/35	2	P	D	Well
		(10 units)					
	3	0	
	4	P	
	5	0	0	
6/ 3/35	1	0	0	0	
9/10/35	1	0	0	
12/ 3/36	1	0	0	
3/ 4/40	2	0	0	
	6	0	0	

Physical examination on March 15, 1935, two weeks after the acute illness, gave entirely normal results. There was no generalized enlargement of lymph nodes; the spleen was not palpable, and the hymen was intact. At the time of the first symptoms the white blood cell count was 8,600, and the differential count revealed 62 per cent neutrophils, 4 per cent eosinophils, 30 per cent lymphocytes and 4 per cent monocytes. The test for heterophil antibody was not done at the time the patient gave positive serologic reactions for syphilis; however, one several weeks later gave a negative result. The serologic tests are summarized in table 8.

CASE 9.—A single white woman aged 19, a student, applied for admission to an out-of-town nurses' training school on Aug. 5, 1939. Her routine physical examination showed nothing significant, but the routine serologic tests for syphilis gave positive results. She gave no history of a syphilitic infection, nor had she had any sexual exposures. Two weeks before her first serologic tests were done she had a sore throat, which lasted about three days. She consulted her family physician, who noted a white patch on the left tonsil but no enlargement of the lymph node. She does not think she had fever at this time.

11. Stryjecki, T.: Ueber die positive unspezifische und vorübergehende Wassermann-Reaktion, Wien. klin. Wchnschr. **51**:1131 (Oct. 14) 1938.

She was examined here on September 20, at which time she was completely asymptomatic. Results of the physical examination showed nothing abnormal, and the hymen was intact. The temperature was 99.2 F. The red blood cell count was 4,980,000; the white blood cell count was 11,950, and the differential count revealed 65 per cent neutrophils, 2 per cent eosinophils, 20 per cent lymphocytes, 12 per cent monocytes and 1 per cent myelocytes. The sedimentation rate was 4 mm. in one hour. The urine was normal. The test for heterophil antibody gave a negative result. The reactions to serologic tests done on her mother and father were negative. The serologic tests on the patient are summarized in table 9.

TABLE 9.—*Serologic Tests for Syphilis, Case 9*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation	Eagle Micro-flocculation	Clinical Findings
7/23/39	Sore throat; no fever?
8/ 5/39	1	P	0	Well
9/ 7/39	2	0	0	
	1	P	0	
	3	P	0	
10/20/39	4	P	0	
	5	P	0	D	..	
		(7.5 units)				
	5	0	0	0	..	Well
4/ 4/40	6	0	0	
	5	0	0	0	..	

TABLE 10.—*Serologic Tests for Syphilis, Case 10*

Date	Laboratory	Wassermann	Eagle Microfloc-culation	Spirochetal (Pallida)	Clinical Findings
4/17/39	1	..	0	..	Sore throat; fever; test for heterophil antibodies positive 1:128
	2	P	0	0	
4/24/39	2	0	0	..	

CASE 10.—A single white woman aged 25, a student, was admitted to the hospital on April 17, 1939, because of a sore throat and a temperature of 101.4 F. There was no history of syphilitic infection. Physical examination showed nothing significant except a red pharynx, with grayish exudate in both tonsillar fossae. A few moist rales were heard at the base of the left lung, but the roentgenogram of the chest was reported as normal. Laboratory examinations on April 17, 1939, yielded data as follows: A smear from the exudate in the tonsillar fossae showed many Vincent's organisms. The red blood cell count was 4,050,000; the hemoglobin content, 15 Gm. per hundred cubic centimeters; the white cell count, 9,840, and the differential count, 9 per cent juvenile neutrophils, 41 per cent neutrophils, no eosinophils, 1 per cent basophils, 6 per cent monocytes and 43 per cent lymphocytes. The test for heterophil antibody gave a positive reaction in a dilution of 1:128. The Wassermann reaction was positive, and the result of the Eagle flocculation test was negative. On April 24, 1939 the test for heterophil antibody was

repeated, and again the result was positive in a dilution of 1:128. The white blood cell count on this date was 7,400, and the differential count, 4 per cent juvenile neutrophils, 21 per cent neutrophils, no eosinophils, no basophils, 8 per cent monocytes and 67 per cent lymphocytes. Many lymphocytes typical of the cells occurring in cases of infectious mononucleosis were seen in the smear. The serologic tests are summarized in table 10.

Cases 8, 9 and 10 had one factor in common, sore throat. Unfortunately, the patients in cases 8 and 9 were not seen by us at the time of the acute infection, nor did they have tests for heterophil antibody done at that time. Both of them may have had some type of sore throat other than that associated with infectious mononucleosis. Case 10 was undoubtedly one of infectious mononucleosis. The test for heterophil antibody gave a positive result in a dilution of 1:128, and the blood smear was typical for that disease.

From a review of the cases reported in the literature it is apparent that no particular cause of sore throat is associated with biologic false positive serologic reactions for syphilis. At least 14 cases of biologic false positive serologic reactions for syphilis associated with scarlet fever have been reported. In 1 of Kissmeyer's¹⁰ 10 cases, in 3 of Krag and Lønberg's⁷ 53 cases and in 5 of Eldh's⁶ 52 cases of nonspecific reactions, sore throat was the only abnormal physical finding, with the exception of the elevation of temperature. In no case was the organism producing the sore throat mentioned. It is possible that our cases 8 and 9 belong in the same group with these 9 just mentioned.

Infectious mononucleosis has repeatedly been reported as a cause of false positive serologic reactions for syphilis. The following authors have reported from 1 to 6 cases each: Löhe and Rosenfeld,¹² Radford and Rolleston,¹³ Weber,¹⁴ Weber and Bode,¹⁵ Bernstein,¹⁶ Priest,¹⁷ Wawersig,¹⁸ Hatz¹⁹ and Sadusk.²⁰ Gooding²¹ discussed the main

12. Löhe, H., and Rosenfeld, H.: Ueber Monozytenangina mit anschliessendem vorübergehend seropositiven Erythema nodosum, zugleich ein Beitrag zur Differentialdiagnose zwischenluetischer und nichtluetischer Angina, *Dermat. Ztschr.* **53**: 373 (April) 1928.

13. Radford, M., and Rolleston, J. D.: Two Cases of Glandular Fever Simulating Typhus, *Lancet* **2**:18 (July 5) 1930.

14. Weber, F. P.: Glandular Fever and Its Lymphotropic Blood Picture, M. Press **130**:65 (July 23) 1930.

15. Weber, F. P., and Bode, O. B.: Beiträge zum "Drusenfieber," *München. med. Wchnschr.* **78**:1589 (Sept. 18) 1931.

16. Bernstein, A.: Antibody Response in Infectious Mononucleosis, *J. Clin. Investigation* **13**:419 (May) 1934.

17. Priest, R.: Glandular Fever, *J. Roy. Army M. Corps* **65**:159 (Sept.) 1935.

18. Wawersig, R.: Ueber unspezifisch-positiven Ausfall der Luesreaktionen im Serum bei der Monozytenangina, *Med. Klin.* **33**:1737 (Dec. 28) 1937.

clinical and laboratory features of 27 cases of infectious mononucleosis and stated:

The Wassermann reaction and the Sigma and Kahn reactions show many interesting features. For the first three to four weeks of the illness 16 of the 27 cases gave either a positive or incompletely positive Wassermann reaction. Those cases which showed a negative Wassermann reaction, in most instances showed a positive Kahn test. The Sigma test, however, was mostly negative.

Poole and Findlay²² stated, "The Wassermann reaction is positive in about half the number of cases. It usually becomes positive in the second week, persists for some weeks and then becomes negative." Bernstein²³ reported positive serologic reactions for syphilis in 6 of 37 cases of infectious mononucleosis. He was unable to find any correlation between the results of the Paul-Bunnell test and the serologic reactions for syphilis. Wassermann titers were tabulated in the 6 cases; in 1 instance the titer was as high as 150 units. In a later article, completely reviewing the subject of infectious mononucleosis, Bernstein²⁴ stated that of the 44 patients he had seen, 18 per cent of those for whom serologic tests were performed had biologic false positive reactions. He expressed the belief that the positive reaction is transitory, rarely occurs over a period longer than three months and generally reverts to negative before the end of the third week of the disease.

CASE 11.—A single white man aged 20, a laboratory assistant, had worked for six months prior to the present illness as an animal boy in the medical school. On Oct. 3, 1937, while cleaning a rat cage, he was bitten on the ring finger of the left hand by a large rat. Within a few days the wound became infected, and on October 6 he noted red streaks running up his hand and forearm. At this time he came to the surgical accident room for treatment and was given 1,500 U. S. P. units of tetanus antitoxin. On admission to the hospital, on October 6, the temperature was 99.4 F. The results of serologic tests for syphilis were negative at this time. The rat bite was treated by soaking, and the local infection subsided. On October 11, the patient's temperature rose to 104.4 F., and a maculo-

19. Hatz, B.: The Wassermann Reaction in Infectious Mononucleosis, with a Report of a Case with Unusual Clinical Features, *Am. J. Clin. Path.* **8**:39 (Jan.) 1938.

20. Sadusk, J. F.: Temporarily Positive Kahn and Wassermann Reactions in Infectious Mononucleosis: Report of a Case, *J. A. M. A.* **112**:1682 (April 29) 1939.

21. Gooding, S. E. F.: On Glandular Fever or Infectious Mononucleosis, *Practitioner* **127**:468 (Oct.) 1931.

22. Poole, L. T., and Findlay, H. T.: Laboratory Diagnosis of Glandular Fever (Infectious Mononucleosis), *J. Roy. Army M. Corps* **66**:145 (March) 1936.

23. Bernstein, A.: False-Positive Wassermann Reactions in Infectious Mononucleosis, *Am. J. M. Sc.* **196**:79 (July) 1938.

24. Bernstein, A.: Infectious Mononucleosis, *Medicine* **19**:85 (Feb.) 1940.

papular rash developed, predominantly on the feet, elbows and wrists and to a lesser extent on the knees, thighs and forearms. There were a few scattered lesions over the skin of both flanks and over the back. Several of the lesions contained small vesicles. The epitrochlear and the axillary glands were palpable on the left side. Except for the rash and a soft, short systolic murmur heard at the cardiac apex and transmitted to the base of the heart, the physical findings were essentially irrelevant.

On Oct. 6, 1937 the white blood cell count was 14,000; the hemoglobin concentration, 14.7 Gm. per hundred cubic centimeters, and the differential count, 87 per cent neutrophils and 13 per cent monocytes. On October 12 the white cell count was 8,600, and the differential count, 16 per cent juvenile neutrophils, 48 per cent neutrophils, 1 per cent eosinophils, 26 per cent lymphocytes and 9 per cent monocytes. On October 10 the results of serologic tests for syphilis were negative; they were also negative when repeated on October 14. On November 1, however, the Eagle flocculation test and the Wassermann test both gave positive results.

TABLE 11.—*Serologic Tests for Syphilis, Case 11*

Date	Laboratory	Wassermann	Eagle Micro-flocculation	Clinical Findings
10/ 3/37	Finger bitten by rat
10/10/37	1	..	0	Slight fever; local lesion healed
10/14/37	1	..	0	Fever; maculopapular rash
11/ 1/37	1	P	P }	Slight fever; rash disappeared Oct. 28; neoarsphenamine started Nov. 2
11/ 3/37	1	P	P }	
11/ 8/37	1	D	D }	Well
11/15/37	1	0	D }	
11/23/37	1	0	P	Relapse; chills
1/ 6/38	1	0	0 }	Well
3/ 7/38	1	0	0 }	
2/ 6/39	1	..	0 }	
3/ 7/39	1	0	0 }	
4/11/39	1	0	0 }	

Unsuccessful attempts were made to demonstrate *Spirochaeta morsus muris* in the blood by dark field examination. Mice were given injections of the patient's blood, but *S. morsus muris* could not be recovered. The rash disappeared October 28, and the patient became afebrile November 8. He was given 0.3 Gm. of neoarsphenamine on November 2 and again on November 9; the dose was increased to 0.6 Gm. on November 16. He was discharged from the hospital at this time, apparently asymptomatic. His temperature was normal, and he felt strong again. He returned to the hospital on November 22 complaining of chills, fever and weakness. His temperature at this time was 104.6 F. Undoubtedly he had a relapse. Physical examination showed nothing abnormal. He was given 0.6 Gm. of neoarsphenamine on November 22 and on December 3, 10 and 24. There was no relapse after this treatment. Serologic tests are summarized in table 11.

Although *S. morsus muris* was not isolated from the patient's blood in this case, the clinical picture was typical of rat bite fever.

There is some difference of opinion as to whether biologic false positive reactions to serologic tests for syphilis occur in rat bite fever.

Bayne-Jones,²⁵ in reviewing 81 cases reported in the United States from 1839 to 1930, stated:

It has often been said that the Wassermann reaction is positive in rat-bite fever. . . . The results of this test were recorded in eighteen cases. Of these, fifteen were negative and three were positive. In each of these three cases, there was the possibility of a coincident syphilis.

On the other hand, Clément²⁶ found positive results in 14 of 26 patients whose serum was tested for syphilis. He expressed the opinion that this proportion of positive results was too high to be interpreted as the result of coincidental infection with rat bite fever and syphilis. Laignel-Lavastine and his associates²⁷ reported a case of rat bite fever in which the blood Wassermann reaction was positive during the febrile period of the disease and became negative within a few days after the temperature returned to normal. The Wassermann reaction of the cerebrospinal fluid was repeatedly negative. Labougle²⁸ reported 1 case of rat bite fever in which there was a false positive reaction for syphilis. Edelman and Haber⁸ reported the cases of 3 children with rat bite fever and false positive serologic reactions for syphilis. The family of each child was carefully investigated and was found to be nonsyphilitic.

Woolley²⁹ reported 1 case, that of a child who had several positive reactions to Hinton tests during the course of the febrile period of rat bite fever. The family of this child was also investigated; the mother and father did not have syphilis. Ledingham³⁰ reported 5 cases of rat bite fever. Serologic tests for syphilis were done in 3 cases, and in only 1, the case of a child whose mother and father did not have syphilis, was there a biologic false positive reaction.

COMMENT

These 11 examples of positive serologic reactions occurring in patients with diseases other than syphilis have been selected from a series of approximately 200 such cases observed by us during the past fifteen

25. Bayne-Jones, S.: Rat-Bite Fever in the United States, *Internat. Clin.* **3**:235 (Sept.) 1931.

26. Clément, R.: Contribution à l'étude des spirochètes, le sodoku, Thesis, Paris, 1923, p. 72.

27. Laignel-Lavastine, Boutet and others: Un cas typique de sodoku à Paris, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:105 (Feb.) 1924.

28. Labougle: Eléments d'observation complémentaires au sujet d'un cas de spirochètose par morsure de rat (sodoku): (Wassermann; formules sanguines), *Soc. de méd. mil. franç., Bull. mens.* **19**:14 (Jan.) 1925.

29. Woolley, P. V.: Rat-Bite Fever: Report of a Case with Serologic Observations, *J. Pediat.* **8**:693 (June) 1936.

30. Ledingham, R. S.: Rat-Bite Fever (Sodoku): Report of Five Cases, *Am. J. Clin. Path.* **8**:333 (May) 1938.

years. The conditions reported are a subacute infection of unknown cause (case 1), acute labyrinthitis of unknown cause (case 2), vaccinia (case 3), pneumonia (caused by *Pneumococcus* type IV in case 6 and by an undetermined agent in cases 4, 5 and 7), sore throat of unknown cause (cases 8 and 9), infectious mononucleosis (case 10) and rat bite fever (case 11).

Quantitative titrations of reagin content were performed in 16 cases. The titer was low (1 to 16 units) in 4 and high in 2 (cases 5 and 8). In both of the latter cases, the serum reagin titer on one occasion was 100 units, a titer comparable with that observed in the early stages of syphilis.

Our material clearly offers no clue to the incidence of biologic false positive serologic reactions in conditions or diseases other than syphilis. Indeed, for lack of serial (preferably daily) testing in cases of acute infectious diseases, this type of information is not available for any disease except malaria.

Justification for the publication of such a heterogeneous series of case reports as this lies in the fact that attention is once again directed to the nonspecificity of serologic tests for syphilis and to the caution necessary in their interpretation. This nonspecificity extends to nearly all the usual serologic technics, e. g., in the cases here reported, the complement fixation (Wassermann) and the flocculation (Kahn, Kline, Eagle, Hinton and Laughlen) tests. Not included in this statement, however, is the complement fixation test with spirochetal antigen (recorded in the tables as "pallida" test), which has as yet not been adequately studied with reference to nonsyphilitic diseases. There is already evidence that the reaction to this test is usually negative in cases of leprosy, in which other serologic reactions are positive,³¹ but that in cases of malaria it is usually positive simultaneously with other positive serologic reactions.³² In 2 of our patients (cases 5 and 10) the pallida reaction was negative at a time when other serologic reactions were positive. The "pallida" test may, like the Kahn verification test,³³ prove useful in the differentiation of positive serologic reactions due to syphilis and those due to other conditions.

31. Cappelli, E.: La "pallidareazione" di Gaetgens sui sieri lebbrosi; contributo allo studio dell'essenza della r. Wassermann, *Gior. di batteriol. e immunol.* **22**:425 (March) 1939. Eagle, H.; Hogan, R. B.; Mohr, C. F., and Black, S. H.: On the Reactivity of the Serum and Spinal Fluid of Leprous Patients with Spirochetal Suspensions, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:397 (July) 1941.

32. Heinemann, H.: Untersuchungen mit der Pallidareaktion, *Dermat. Wchnschr.* **94**:680 (May 14) 1932; Ueber die praktische Brauchbarkeit der Pallidareaktion im Arbeitskreis des Tropenarztes, *Arch. f. Schiffs- u. Tropen-Hyg.* **36**:9 (Jan.) 1932.

33. Kahn, R. L.: A Serologic Verification Test in the Diagnosis of Latent Syphilis, *Arch. Dermat. & Syph.* **41**:817 (May) 1940.

It seems only fair to suggest that in the absence of a healthy skepticism as to the specificity of serologic tests for syphilis, several at least of the patients whose cases are here reported might well have been given unnecessary treatment for syphilis.

Biologic false positive serologic reactions occurring not only in persons with nonsyphilitic diseases but in normal persons as well³⁴ require particular emphasis in view of the ever increasing use of routine serologic tests in medical practice, industry and compulsory premarital and antepartum examinations.

SUMMARY

We have reported the cases of 11 nonsyphilitic patients with various diseases in whom transitory biologic false positive serologic reactions for syphilis were observed.

When analyzed quantitatively, a low titer was usually revealed in these tests, but in the tests on 2 patients, 1 with a sore throat and 1 with pneumonia, a high titer, comparable to that seen in the early stages of syphilis, was observed.

It is suggested that a complement fixation test with spirochetal antigen (pallida test) may be helpful in differentiating false from true positive reactions.

In view of the enormous increase in the routine use of serologic tests for syphilis, the necessity for caution in their interpretation is emphasized.

34. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: I. Occurrence in Normal Persons, *Arch. Int. Med.* **68**:898 (Nov.) 1941.

PULMONARY CAVITATION ASSOCIATED WITH COCCIDIOIDAL INFECTION

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That the roentgenographic appearance of pulmonary coccidioidal infection may closely simulate that of pulmonary tuberculosis has been pointed out repeatedly, particularly by Smith,¹ Yegian and Kegel² and Farness and Mills.³ When pulmonary cavitation occurs the mimicry is even more striking, and confusion in diagnosis may follow unless the causative organism is first isolated and identified. It would appear, however, that such parallelism between the two infections exists only in roentgenograms. Coccidioidal cavitation, as demonstrated in the 13 cases reported in this paper, is far more benign than is pulmonary cavitation due to tuberculosis. Unlike the latter condition, which usually occurs during reinfection or in the adult type of the disease, most coccidioidal cavitation develops during or shortly after the primary stage of pulmonary infection. This belief was also expressed by Farness and Mills in their first report of a case of pulmonary cavitation due to coccidioidal infection.

The prognosis in cases of primary coccidioidal cavitation is entirely favorable. Prolonged hospitalization or care in a sanatorium is unnecessary, and patients with this condition may be returned early to unrestricted lives and permitted to continue with their usual occupations, despite the existence of a typical "burned out," or pathologically latent, pulmonary coccidioidal cavity. It is especially important not to resort to extraordinary collapse procedures or thoracic surgery in attempting to close such cavities. Exception may be made and pneumothorax performed if hemoptysis occurs frequently or in large amounts or if the primary cavitation may appear to be in a more active phase than the characteristic thin-walled, residual cavities described here.

1. Smith, C. E.: Parallelism of Coccidioidal and Tuberculosis Infections, read at the Clinical Section at the Annual Meeting of the California Tuberculosis Association, April 5, 1941.

2. Yegian, D., and Kegel, R.: *Coccidioides Immitis* Infection of the Lung, *Am. Rev. Tuberc.* **41**:393 (March) 1940.

3. Farness, O. J., and Mills, C. W.: *Coccidioides* Infection, *Am. Rev. Tuberc.* **39**:266 (Feb.) 1939.

From the standpoint of public health, patients with coccidioidal infection cannot be considered a menace to society, as are those with tuberculosis. Investigators are in general agreement that infection is produced by the chlamydospores of the fungus (reproductive cycle). Acute infection does not pass from person to person via sputum containing the endospores or spherules (parasitic phase). The natural occurrence of the fungus in the soil of areas in which this disease is endemic has been demonstrated. When climatic conditions favor the formation of dust and winds (dry seasons), the infectious chlamydospores, being numerous and light, are easily transported and inhaled and may produce respiratory infection in nonimmune persons. Occasionally, the infectious agent may enter via cuts or abrasions of the skin.

From the clinical standpoint there is striking absence of severe constitutional symptoms despite the existence of pulmonary cavitation, hemoptyses or spherule-laden sputum, so that again one recognizes a paradoxical relation between coccidioidal cavitation and symptomatology.

It is therefore important to bear in mind the possibility of coccidioidomycosis whenever pulmonary cavitation occurs and tubercle bacilli have not been demonstrated, especially when the patient has resided in an area where the disease is endemic. Such regions at present are the San Joaquin Valley and nearby valleys in central California, parts of Arizona and Texas and the Chaco regions of Argentina. Increasing ease of travel and shifting populations will undoubtedly produce a proportionate increase in cases of coccidioidomycosis elsewhere than in these areas.

Acute primary coccidioidomycosis (San Joaquin fever, valley fever, desert rheumatism) was described by Dickson and Gifford in 1938⁴ and its epidemiology presented by Smith in 1940.⁵ The extent of coccidioidal infection among the residents of the San Joaquin Valley is indicated by the large proportion of the population giving a positive cutaneous reaction to coccidioidin. Gifford⁶ and her associates, who carried out an extensive skin-testing survey in the schools in Kern County, Calif., found that over half of 2,718 children gave a positive cutaneous reaction. The percentage rose from 17 per cent for those with residence under one year to 77 per cent for those with residence of ten years or more. In the town of Maricopa, where most of the children tested were native, 84 per cent reacted. Of 110 students of the Porterville High School freshman class, 76 (70 per cent) reacted to coccidioidin. Of this

4. Dickson, E. C., and Gifford, M. A.: Coccidioides Infection (Coccidioidomycosis), *Arch. Int. Med.* **62**:853 (Nov.) 1938.

5. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum, *Am. J. Pub. Health* **30**:600 (June) 1940.

6. Gifford, M. A.: Coccidioidomycosis, Kern County, Session on Fungus Infections, *Proc. Sixth Pacific Sc. Cong.*, 1939, p. 74.

number, only 1 gave a history of erythema nodosum; there was no evidence of coccidioidal granuloma.

Definite evidence of such widespread primary coccidioidal infection, with the probable exception of calcification, is difficult to obtain by an ordinary roentgen examination of the chest. In this respect there exists the same difficulty one encounters in identifying primary tuberculous infection. However, when primary pulmonary coccidioidal infection is manifested by residual cavitation, it should be easily recognized by fluoroscopy alone.

That residual pulmonary coccidioidal cavitation must be regarded as only an infrequent manifestation of the primary coccidioidal infection is borne out by six years' experience in fluoroscopic and roentgen examination of many residents of San Joaquin Valley. However, one must acknowledge that in an unknown number of cases the primary coccidioidal cavities close spontaneously, as illustrated in 4 of the cases reported. Pulmonary cavitation associated with early primary coccidioidomycosis must, therefore, occur more often than would be indicated by the small percentage of latent pulmonary cavities discovered among Valley residents. Coccidioidal granuloma remains a relatively uncommon disease and must not be confused with primary coccidioidomycosis. Pulmonary cavitation in association with granuloma is unusual. There should be no difficulty in differentiating between the two diseases or between the forms of cavitation associated with them.

Primary infection by *Coccidioides immitis* is commonly accompanied by symptoms referable to the respiratory tract, usually bronchitis with a slightly productive cough. Associated with these may be malaise, anorexia, chills, fever, headache, backache, night sweats and pleurisy. Roentgenograms of the lungs taken at this stage may reveal only changes in the area of the lung root, such as peribronchial haziness, or there may be definite patches of pneumonitis, which often assumes a nodular form. Occasionally, exudative lesions involving lobules, or even entire lobes of the lung, are present and may be associated with early cavitation. Recovery is followed by a walling off or clearing of the primary focus without complication. Evidence of the first infection may remain and be revealed in the roentgenogram in the form of localized caseous or calcified foci or cavitation. Bacteriologic studies of the sputum during the acute stage of the disease will reveal the presence of the spherules of *C. immitis*. Seven to fourteen days after such infection has occurred cutaneous sensitivity to coccidioidin will develop. In 2 to 5 per cent of the cases erythema nodosum or erythema multiforme will occur, usually appearing five to fourteen days after the onset and persisting for one to four weeks. Occasionally, pleurisy with effusion occurs and the organism can be recovered from the pleural fluid. That primary infection is possible with few or no recognizable symptoms is also to be

accepted, as indicated by the high percentage of reactors to coccidioidin among residents of San Joaquin Valley.

As has been stated, there may be few or no symptoms associated with residual coccidioidal pulmonary cavitation after the acute primary infection has subsided. For this reason 2 cases (1 and 4) were discovered only by chance. When cavitation occurs in conjunction with the acute primary infection (case 11), the clinical picture differs little from the one just described. However, in most (9 of 13) of the cases in this series the patients gave a definite history of hemoptysis, varying from frequent streaking to frank hemorrhage, which caused them to seek medical advice. In 2 cases pulmonary bleeding followed moderately severe physical exertion. In others it was apparently aggravated by acute infection of the lower respiratory tract. In about half of the cases there was a history of one or more respiratory infections, occasionally resulting in a fairly prolonged period of cough and expectoration. Chronic expectoration often appeared as only a slight amount of mucoid material raised in the morning, which increased during respiratory infections or "colds" and then was occasionally streaked with blood. That involuntary or unrecognized production of sputum occurred is illustrated in case 3, in which gastric lavage was necessary to demonstrate the fungus. All patients with latent cavitation (cases 1 to 10) appeared in good health. While they were under observation in the hospital they had no persistent elevation of temperature, pulse rate or respiratory rate. They were able to follow ordinary occupations except when forced to stop work because of recurrent pulmonary hemorrhage (cases 5 and 9).

In describing these cavities the term "latent" has been used to imply that the lesion is no longer progressive but has become arrested and quiescent. The term "healed" could not be applied because these cavities harbor viable *C. immitis*. Immunity must be produced in the host by the primary infection. Otherwise, because of the prevalence of coccidioidal infection, residents of San Joaquin Valley would invariably die after fairly short stays in the valley. This concept explains best the paradox of persisting pulmonary coccidioidal cavitation without dissemination of the disease, despite the role played by the cavity as a reservoir or incubator for the causative fungus.

Criteria for the diagnosis of latent coccidioidal pulmonary cavitation were based on the roentgenographic appearance of a thin-walled cavity, which appeared "punched out" or "dead," with little or no surrounding collateral reaction. An accompanying clinical history of hemoptysis and occasional infection of the lower respiratory tract, with a slightly productive cough, was usually obtained from the patient, who otherwise seemed well. Cutaneous sensitivity to coccidioidin was demonstrated in all cases

by the intracutaneous test.⁷ Careful bacteriologic studies of sputum or gastric contents by Dr. C. E. Smith and associates,⁸ of the Department

7. The cutaneous test was made, read and recorded by the method used for the Mantoux tuberculin reaction. The peak of reaction generally occurs thirty-six hours after injection of coccidioidin; in this study the reading was made at the end of forty-eight hours. The result has the same significance as the result of the tuberculin test; i. e., a positive reaction indicates present or past infection with *C. immitis*.

The coccidioidin used in testing was prepared by Dr. C. E. Smith. The synthetic medium (containing but 2.5 per cent glycerin) approved by the Bureau of Animal Industry was inoculated with multiple strains of *C. immitis*. After incubation at 37 C. for two months it was made up to volume with one-tenth its volume of a solution of merthiolate and distilled water (1:1,000), filtered through a Berkefeld or Seitz filter and tested for sterility and potency.

Dilutions from 1:10,000 to 1:100 were used, according to the reaction produced. Control tests were also made to rule out sensitivity to glycerin or to other material contained in the medium. Great caution was observed in using needles, syringes and sterilizing pans that had never been used for tuberculin testing. The test is highly specific with dilutions down to and including 1:100. For patients with granuloma it may finally be necessary to use a dilution of 1:10, and terminally patients with this condition may become anergic.

8. Absolute proof of the presence of *C. immitis*, according to Smith and co-workers (Smith, C. E.; Wheatlake, R. J.; Chern, N.; Lack, A. R., and Baker, E. E.: *Diagnosis of Coccidioidal Infection by Recovery of Coccidioides Immitis*, to be published), is provided by (1) observation in tissue sections of characteristic double-contoured spherules with endospores and without budding and (2) recovery of the mycelial form by culture and demonstration of spherules in inoculated animals. The following method was used: Sputum, gastric contents or contaminated pus is treated with a 0.05 per cent solution (final concentration) of cupric sulfate. (To prevent solution of spherules gastric contents should be neutralized if allowed to stand for any length of time. Alkaline digestants used in concentrating specimens also rapidly dissolve the endospores.) After it has stood four hours, the suspension is centrifuged. The sediment is examined microscopically in a fresh cover slip preparation and is planted on Sabouraud's medium (to which has been added a 0.05 per cent solution of cupric sulfate) and on a blood agar plate. (A differential medium which was found useful consists of 1 per cent ammonium chloride, 1 per cent sodium acetate, 0.8 per cent tribasic potassium phosphate, 0.04 per cent cupric sulfate and 2 per cent agar.) The plates are incubated at 37 C., and the sediment is placed in the ice box. If the blood agar shows a few colonies the next day the sediment is suspended in a solution of sodium chloride and inoculated intratesticularly into a guinea pig. If many colonies appear, another blood agar plate is inoculated and the procedure is repeated the following day.

The guinea pig is killed after one month (after two weeks if the testicle becomes enlarged), and tissues are examined for spherules and cultured on Sabouraud's medium and/or on the differential medium. If the guinea pig tissues are negative for *C. immitis* but the culture shows a growth of white fungus suspiciously like coccidioides, the fungus is suspended in a saline solution and inoculated into a guinea pig intratesticularly or a mouse intraperitoneally. The lungs and the omentum should be examined with great care if a mouse is used.

Hanging drop preparations of spherules are also useful for observing their characteristic method of sprouting.

of Public Health, Stanford University School of Medicine, disclosed the presence of *C. immitis*. Serologic studies of the blood were usually confirmatory.⁹ In no case did clinical observation or roentgen follow-up studies, varying from a few months to several years, disclose any evidence of dissemination of the infection or progression of the disease (cases 1 to 13).

REPORT OF CASES

CASE 1.—C. M., a 19 year old single Portuguese farm worker, had been a resident of Kings County (San Joaquin Valley) since birth.

First Admission (April 8, 1936 to May 16, 1937).—The patient had been in generally good health until Jan. 13, 1936, when, after an automobile accident, he noted persistent pain in the right side of the chest and went to his family physician for examination. After roentgen examination of the chest the patient was informed that he had tuberculosis. There was no history of chronic cough or expectoration, although a short time previous to admission he had raised a small amount of sputum in the early morning. He stated the belief that he had had some thoracic pain on the right side previous to the accident and also that he had been tiring more than usual and that his strength was not as good as usual. His physician had reported a temperature of 99 to 100 F. in the afternoon, with a pulse rate of 78 to 90 beats per minute. The patient was referred to the hospital at Springville and admitted on April 8.

Past History: The patient had had the usual childhood diseases. He had never had erythema nodosum or erythema multiforme and to his knowledge had never been exposed to tuberculosis.

Physical Examination: The patient was a well developed, swarthy youth who did not appear acutely ill. No abnormal thoracic signs could be elicited. For the first few weeks the temperature was elevated in the afternoon to a maximum of 100.2 F.; the pulse rate varied from 64 to 90 beats per minute.

Examination of the blood revealed the red cell count was 4,930,000, the white cell count 11,950, with 72 per cent polymorphonuclears and 28 per cent lymphocytes, and the hemoglobin concentration (Tallqvist) 100 per cent. Both the red and white cells were normal in appearance. The Wassermann reaction of the blood was negative on April 11. Five specimens of sputum, including a concentrated twenty-four hour specimen, were negative for tubercle bacilli. Previous to admission, a single specimen of sputum had been reported by the patient's local physician as negative for tubercle bacilli.

A roentgenogram of the chest (fig. 1 *A*) taken by the local physician on March 2, prior to admission, revealed a cavity measuring 5 cm. in diameter beneath the right infraclavicular area, with considerable surrounding reaction. This was interpreted as a tuberculous cavity, with surrounding tuberculous infiltration of exudative type. A second roentgen examination approximately five weeks later, following admission, again disclosed the cavity, now smaller, with much less surrounding reaction (fig. 1 *B*).

9. The serologic tests were performed by Dr. Smith and his associates, who used coccidioidin as an antigen. The results of the serologic studies, which will be reported in another paper, indicate that complement is fixed in a high titer in cases of coccidioidal granuloma but is fixed only in low dilutions in cases of latent coccidioidal pulmonary cavitation. Precipitins, also, give only a low grade reaction in cases of the latter disease.

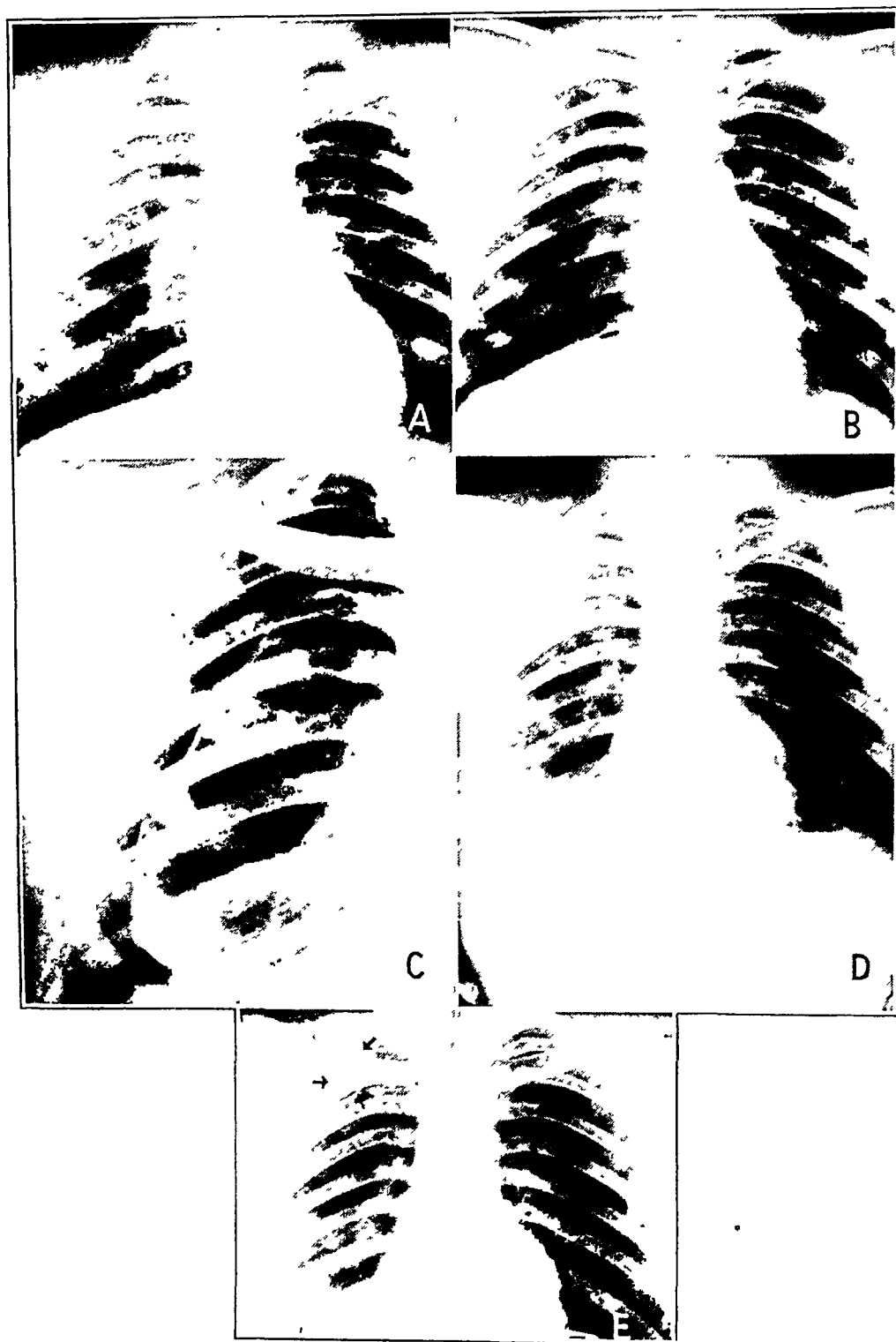


Fig. 1.—Case 1 (C. M.). Roentgenograms taken (A) March 2, 1936, (B) April 9, 1936, (C) Dec. 3, 1937, (D) May 15, 1940 and (E) Nov. 20, 1940.

Course of Illness: The patient was confined to bed, and despite the absence of tubercle bacilli in the sputum, pneumothorax treatment was started on the right side on April 9. A fairly selective collapse of the upper lobe was obtained, but the previously described cavity remained, with little evident change in size; complete collapse was prevented by a long broad adhesion beneath the second interspace. Peripheral reaction about the cavity was only slight. Because of the failure of the cavity to close, the right phrenic nerve was crushed on August 2; subsequently the right side of the diaphragm rose approximately one interspace.

Discharge: The patient left the hospital on May 16, 1937, with his clinical condition entirely quiescent. He had gained $11\frac{3}{4}$ pounds (5.4 Kg.) in weight. Pneumothorax refills were continued in the outpatient clinic.

Second Admission (Jan. 18, 1938 to April 6, 1939).—Because the cavity failed to close under this collapse therapy, the patient was advised to reenter the hospital. A roentgenogram (fig. 1 C) taken Dec. 3, 1937 disclosed the degree of collapse and the patent cavity. While at home he had been doing general ranch work and had not kept regular hours of rest.

He was again confined to bed, and treatment with pneumothorax under moderately positive pressure was instituted. The cavity failed to close, although the patient's clinical condition remained quiescent, without elevation of temperature or pulse rate. On numerous occasions the sputum, examined both by direct smear and by concentration, was negative for tubercle bacilli.

On March 12, 1938, intrapleural pneumolysis was done and the previously described adhesion successfully severed. Despite a regimen of modified rest in bed and continuation of treatment with pneumothorax under slightly positive pressure the cavity remained open. Roentgenograms showed the cavity lying near the periphery of the relaxed upper lobe of the right lung. Severing the adhesion had in no way aided the effectiveness of the collapse.

In September 1938, consultation with Dr. Leo Eloesser was held concerning the necessity of any further surgical treatment, and it was agreed, in view of the inability to demonstrate tubercle bacilli, that the possibility of a solitary pulmonary cyst should be considered. Mantoux tuberculin tests made then with old tuberculin in a dilution of 1:10,000 produced a 2 plus reaction. It was decided to abandon pneumothorax, and the lung was allowed to reexpand slowly. The cavity remained open beneath the outer infraclavicular area and possessed a thin wall, with no surrounding reaction.

The patient was discharged from the hospital on April 6, 1939, and the diagnosis was changed to one of "no definite evidence of pulmonary tuberculosis; probable solitary pulmonary cyst." He was seen at intervals of three months and remained in good health, doing ranch work involving heavy labor. Fluoroscopic and roentgen examination revealed little change in the appearance of the cystlike cavity.

He remained well until May 15, 1940, when he acquired a "chest cold" and a productive cough, which forced him to stop work and resulted in the loss of approximately 11 pounds (5 Kg.) of weight and the onset of easy fatigability. A roentgenogram (fig. 1 D) taken May 15 revealed considerable new exudative reaction occupying the upper half of the right pulmonary field and surrounding the cystlike cavity.

Third Admission (May 17 to Aug. 6, 1940).—He was again admitted to the hospital and was placed on a regimen of modified rest in bed. Neither the temperature, the pulse rate nor the respiratory rate was elevated. A slightly productive cough was present. He stated that the "cold" had improved considerably and that he "was getting over an attack of influenza." A roentgenogram taken three weeks later showed clearing of the exudative reaction. The cavity remained

and apparently contained fluid. On June 9 the patient gave a 2 plus cutaneous reaction to coccidioidin in a dilution of 1:1,000. Stained preparations of sputum remained negative for tubercle bacilli. A specimen of sputum collected on May 24 was reported by Dr. Smith to contain *C. immitis*; a white fungus morphologically like coccidioides was recovered from sputum cultured on several different mediums, from the spherules of *C. immitis* found in large testicular lesions of a guinea pig inoculated with treated sputum and killed June 11 and from spherules found in the lungs of a mouse inoculated with the fungus recovered in the guinea pig.

The patient was discharged to his home on August 6, with the diagnosis "primary coccidioidomycosis, with cavitation."

Roentgen examination on November 20 revealed the clearing about the cavity, which retained its characteristic thin-walled appearance.

On November 26 a sample of blood serum preserved with merthiolate was sent to Dr. Smith, who reported: "Complement was completely fixed in the second tube (1:4) and partially fixed in the next tube."

When next seen in the outpatient clinic, on Jan. 20, 1941, the patient stated that he felt in good health and was again able to work about the ranch. His weight had increased to 186½ pounds (84.7 Kg.). He had had no cough, expectoration or recent "colds" or "influenzal attacks." A roentgenogram taken with the patient in a slightly oblique position revealed the persistence of the cavity in the apex of the right lung, with little change in size, shape or appearance.

When the patient was seen again, June 25, roentgen examination (fig. 1 E) failed to reveal further evidence of the cavity in the apex of the right lung. It had apparently closed spontaneously. Clinically the patient remained well and continued to work. There had been no further infection of the upper respiratory tract.

The roentgenographic appearance of the cavity so closely simulated that of cavitation in a case of tuberculosis that the patient was energetically treated for a long period in a tuberculosis hospital. Recognition of the cavity as one of coccidioidal type was not made until *C. immitis* was demonstrated in the sputum, approximately four years after the patient first came under medical observation. This case also illustrates exacerbation about the cavity, associated with the presence of spherules in the sputum and followed by rapid clearing of the reaction in ten weeks. At the end of five and a half years' observation (September 1941) the pulmonary coccidioidal cavity has apparently closed spontaneously.

CASE 2.—E. D., a 21 year old single American, an ex-enrollee of the Civilian Conservation Corps and telephone construction helper, had resided in Visalia (Tulare County) for seventeen years.

Hospitalization (July 21, 1939 to July 31, 1940).—The patient had been in general good health until one month prior to admission, when he noticed a warm sensation in his throat and without warning coughed up approximately 1 to 2 drachms (4 to 7 cc.) of red blood. The hemoptysis gradually cleared in the course of the next twenty-four hours. For the year and half previous to admission he had noticed slight shortness of breath on exertion and had complained of occasional night sweats. There was no history of chronic cough, expectoration, influenzal attacks, valley fever or erythema nodosum. To his knowledge he had

not been exposed to tuberculosis. His weight had remained fairly stable, at 130 pounds (59 Kg.). He had been referred to the hospital by his physician because of the hemoptysis.

Past History: The past history was irrelevant.

Physical Examination: The patient was a tall, thin, fairly well developed young man who was obviously not ill. Examination of the chest revealed nothing abnormal. The temperature, pulse rate and respiratory rate were within normal limits. Examination of the blood yielded the following data: red cell count, 4,200,000; white cell count, 6,550, with 64 per cent neutrophils, 33 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils; hemoglobin content, 11.5 Gm. per hundred cubic centimeters, and Kline reaction of the blood negative.

A roentgenogram (fig. 2*A*) taken prior to admission, July 8, revealed a prominent cavity in the extreme apex of the left lung, above the clavicle, with little surrounding reaction. The remainder of the lung parenchyma appeared to



Fig. 2.—Case 2 (E. D.). Roentgenograms taken (*A*) July 8, 1939 and (*B*) Feb. 22, 1940.

be clear. A presumptive diagnosis of pulmonary tuberculosis was made on the basis of this roentgenogram.

Course of Illness: On admission the patient was confined to bed. There was no chronic cough, although occasionally he raised a small amount of mucoid sputum, not more than 0.5 drachm (1.9 cc.) per twenty-four hours. On a few occasions this was found to be blood streaked. On numerous occasions the sputum, including concentrated specimens and material obtained by gastric lavage, was negative for tubercle bacilli. Likewise, examination of moist preparations of sputum failed to reveal spherules of *C. immitis*. The patient gave a negative cutaneous reaction to intracutaneous tests with old tuberculin in a dilution as low as 1:100 and to purified protein derivative (second strength). On August 19 he gave a 2 plus reaction to coccidioidin in a dilution of 1:1,000. Unneutralized gastric contents obtained on November 30 were sent to Dr. Smith. Because *C. immitis* could not be demonstrated by direct examination, culture or animal inoculation, the specimen was recorded as negative for this organism on Jan. 4, 1940.

Because of the apical cavitation in the left lung, initial pneumothorax had been started on July 25, 1939. In the next few weeks only a partly effective collapse

was obtained, with the lung remaining suspended at the apex by a few pleural bands. The collapse was continued with refills of 350 to 400 cc. of air, and the patient was permitted modified exercise. After five months a roentgenogram revealed the cavity in the apex was still open, with little decrease in size. On December 29 the patient had a small hemoptysis. The ineffective pneumothorax was discontinued in January 1940. The diagnosis of tuberculosis had not been confirmed, and the existence of another pathologic condition was considered. Throughout repeated examinations in January and February the sputum remained negative for tubercle bacilli. On February 22 iodized poppyseed oil was instilled into the bronchus of the upper lobe of the left lung through a ureteral catheter, with the patient in the horizontal and in the Trendelenburg position. The oil was seen to enter the ascending bronchial tree, then flow into a curious, bluntly dilated sacculæ, which seemed to be curved on itself and was surrounded by a faintly visible peripheral zone forming a halo (fig. 2B). Apparently the oil had flowed in and partly filled a loculated cavity which lay in the extreme upper part of the lobe.

A second specimen of sputum, collected on February 5, was forwarded to Dr. Smith. He and his associates isolated *C. immitis* both by culture and by animal inoculation.

On March 8 a single specimen of sputum prepared by the cover slip method revealed a few double-contoured bodies typical of *C. immitis*. On April 4 the patient had an acute attack of pleurisy at the base of the left lung, which subsided in a few days under conservative treatment. During the remainder of the period of hospitalization he showed little clinical change and resumed exercise.

He was discharged to the outpatient department on July 31. When seen again, on October 8, he had gained in weight and had been working in a garage. One episode of infection of the upper respiratory tract had occurred, associated with cough and production of sputum but with no further hemoptysis. A roentgenogram taken at that time showed persistence of the previously described cystlike cavity in the apex of the left lung, with little change elsewhere in either pulmonary field.

A specimen of sputum taken on Jan. 21, 1941, was forwarded to Dr. Smith, who again isolated *C. immitis*. The patient continued his work in the garage and felt well. A roentgenogram taken January 21 showed only a suggestion of the cavity remaining in the extreme apex of the left lung.

He was last seen on June 21. The pulse rate and temperature were normal. There had been no further cough or production of sputum. Roentgen examination of the chest revealed a small amount of residual fibrosis persisting in the apex of the left lung. The cavity could no longer be outlined and was apparently closed.

The appearance of the cavity in the first roentgenogram, taken July 8, 1939, was typical of latent coccidioidal cavitation. The history of hemoptyses was also suggestive. Instillation of iodized poppyseed oil revealed the trabeculated structure of the cavity and indicated associated bronchial changes. The patient gave negative cutaneous reactions both to old tuberculin and to purified protein derivative. The cavity has apparently closed with the patient under a normal routine of working and living, approximately two years after he first came under roentgen observation. Failure to neutralize the specimen of gastric contents on Nov. 30, 1939 permitted the solution of any spherules present, and *C. immitis* was not isolated until Feb. 5, 1940.

CASE 3.—F. R., a 37 year old American housewife and office worker, had lived in Tulare County (San Joaquin Valley) for fifteen years.

First Admission (July 24 to Sept. 6, 1938).—Seven years before admission the patient had been in an automobile accident and had never felt well since. In May 1931 a cough had developed, which was followed by three pulmonary hemorrhages, during which she had raised from 0.5 to 1 ounce (15 to 30 cc.) of blood. A consultant in San Francisco, to whom her local physician had mailed roentgenograms, had advised that she had bronchopneumonia. She had been confined to bed, where she had remained for six months with steady improvement. The only further symptom had been occasional pain in the right side of the chest which was unrelated to respiration. Thereafter, she had been able to carry on with her ordinary daily duties, including employment as a secretary. There had been no chronic cough or expectoration, but she had noticed blood-tinged sputum on several occasions during "chest colds." At these times she had had some pain in the right side of the chest. She had been referred to the hospital at Springville by her local physician.

Past History: The patient gave a history of influenza in 1922.

Family History: The family history was irrelevant, and to her knowledge she had never been exposed to tuberculosis. She had not had erythema nodosum or erythema multiforme.

Physical Examination: The patient was a thin, apprehensive woman who was not in distress. The left shoulder drooped somewhat. One examiner heard occasional rales in the right axilla, but this was not noted again. Studies of the blood revealed the red cell count was 4,720,000, the white cell count 7,300, with 78 per cent neutrophils, 20 per cent lymphocytes, 2 per cent eosinophils and no monocytes or basophils, and the hemoglobin concentration (Sahli) 98 per cent. The red cells appeared normal; the Kline reaction was negative and the sedimentation curve and rate (Brooks) were normal.

A roentgenogram (fig. 3 A) taken June 11 revealed an elongated, well defined, annular cavity lying beneath the third interspace on the right side, with little surrounding reaction; elsewhere the pulmonary fields were comparatively clear.

Course of Illness: The patient was placed on a regimen of modified rest in bed. Her temperature, pulse rate and respiratory rate remained within normal limits. There was no cough or production of sputum. Except for occasional restlessness she seemed comfortable.

It was felt that the diagnosis lay between a quiescent tuberculous cavity in the base of the right lung and a congenital solitary cyst. Sputum was not available for study. A roentgenogram taken August 11 failed to reveal any change in the appearance of the cavity in the right lung. At her own request the patient was discharged from the hospital on September 6 for continued observation in the outpatient department.

Eight months later she stated that she felt fine and had been generally well. A roentgenogram revealed little change in the appearance of the cystlike cavity in the right lung. There was no evidence of surrounding inflammatory reaction. The patient gave a negative cutaneous reaction to old tuberculin in a dilution of 1:1,000 and a positive reaction (3 plus) to coccidioidin in a dilution of 1:10. The tests with these substances were repeated Dec. 29, 1940, at which time the patient gave a negative reaction to old tuberculin in a dilution of 1:100 and a positive reaction (1 plus) to coccidioidin in a dilution of 1:1,000.

Second Admission (April 3 to 7, 1940).—Iodized poppyseed oil introduced through a bronchial catheter only partly filled an irregularly shaped bronchial defect in the approximate location of the cystlike cavity (fig. 3 B).

She returned to the outpatient clinic on December 29, at which time she stated that she had been feeling well except for a slight attack of influenza in November, which had resulted in a slightly productive cough. A roentgenogram revealed little change in the size, shape or appearance of the cystlike cavity.

Dr. C. E. Smith commented as follows on a specimen of gastric contents taken April 6, 1941: "Cultures on Sabouraud's and on a special differential coccidioides medium yielded a growth of white fungus resembling coccidioides. A white mouse inoculated with the culture on April 9 died May 7, with many pulmonary lesions containing endosporulating spherules. Cultures from the lesions showed a growth of characteristic white fungus on differential coccidioides medium. It is concluded that the specimen submitted contained viable *C. immitis*."

On April 28 Dr. Smith reported the following results of serologic tests: "Complement fixation test: dilution of 1:2, 4 plus; dilution of 1:4, 1 plus. Precipitin test: undiluted, 1 plus; dilution of 1:10, questionable. The serum shows evidence

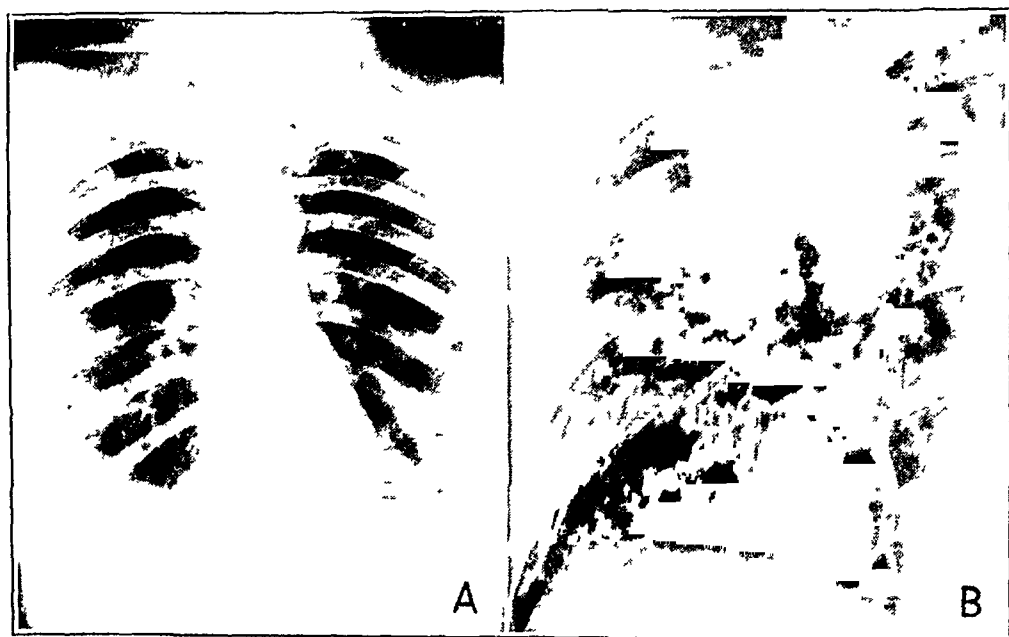


Fig. 3.—Case 3 (F. R.). Roentgenograms taken (A) June 11, 1938 and (B) April 4, 1940.

of infection with *C. immitis* to the degree characteristically seen in patients with a solitary cavity."

A roentgenogram of the chest taken September 24 revealed persistence of the cavity and little change in its appearance. The patient declared that she felt well, had no symptoms of involvement of the respiratory tract and continued to work.

During a period of thirty-eight months' roentgenographic observation the typical thin-walled appearance of the latent coccidioidal cavity remained unchanged. The cavitation produced few symptoms other than the hemoptyses previous to observation and interfered in no way with the patient's occupation. In this case, also, the use of iodized poppyseed oil revealed an associated, localized and minor bronchial defect. The result of the complement fixation test was indicative of a mild, latent infection. *C. immitis* was isolated from neutralized gastric

contents both by culture and by animal inoculation. The patient gave a negative cutaneous reaction to old tuberculin in a dilution of 1:100 and a positive cutaneous reaction to coccidioidin in a dilution of 1:1,000.

CASE 4.—J. H., a 24 year old single American-born Mexican ex-enrollee of the Civilian Conservation Corps and ranch worker, had been a resident of Kings County (Hanford) for eleven years.

First Admission (April 12 to Nov. 30, 1940).—The patient had no specific complaints. He was seen in the chest clinic as a contact who had been exposed to possible tuberculous infection through a tuberculous sister. Fluoroscopic examination had revealed a small cavity in the middle of the left pulmonary field, and the patient had been referred to Springville for hospitalization. On closer questioning, he described occasional pain of two or three months' duration in the left side of the chest and stated he had lost 4 to 5 pounds (2 to 2.5 Kg.) in weight. There was no definite history of cough, expectoration or hemorrhage.

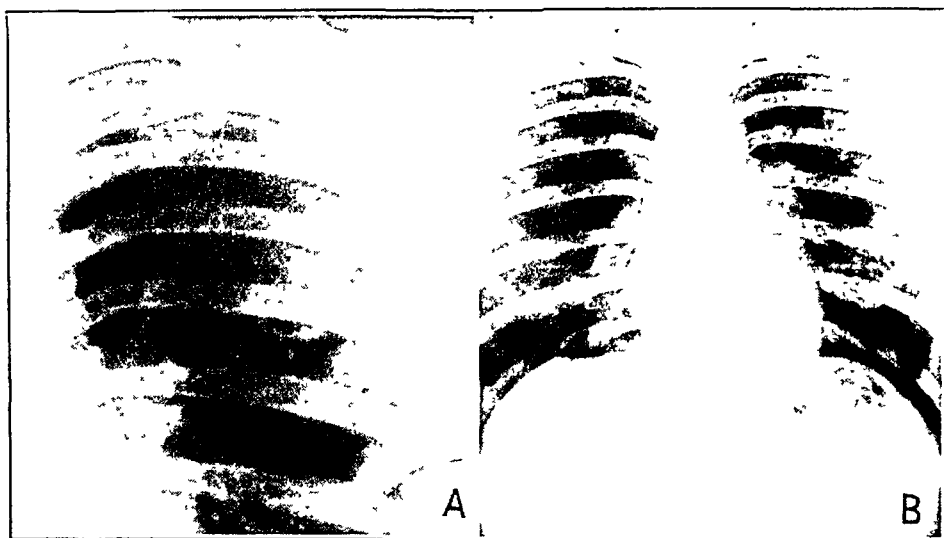


Fig. 4.—Case 4 (J. H.). Roentgenograms taken (A) April 2 and (B) Aug. 24, 1940.

Past History: The patient had had the usual childhood diseases. He had not had valley fever or erythema nodosum or other cutaneous rash.

Family History: In 1939 a sister, aged 29 had died of pulmonary tuberculosis. The patient had had definite contact with her.

Physical Examination: The patient was a healthy-appearing, well nourished man who was obviously not ill. Examination of the chest revealed nothing abnormal except a few inconstant fine rales beneath the left second intercostal space anteriorly. Studies of the blood on admission revealed that the Kline reaction was negative, the hemoglobin content 14 Gm. per hundred cubic centimeters, the red cell count 5,140,000 and the white cell count 9,350, with 65 per cent neutrophils, 31 per cent lymphocytes, 3 per cent eosinophils and 1 per cent monocytes.

A roentgenogram (fig. 4 A) taken at the time of the first examination, April 2, disclosed a distinct, thin-walled cavity, approximately 3 cm. in diameter, beneath the third rib on the left, with little peripheral reaction. A few small calcified foci were noted adjacent to the right descending bronchial tree and in the left hilus.

Course of Illness: After admission the patient was placed on a regimen of modified rest in bed.

On numerous occasions material obtained by gastric lavage, concentrated sputum and sputum inoculated on Petraghani's culture medium were negative for tubercle bacilli.

On April 19 he gave a 2 plus cutaneous reaction to old tuberculin in a dilution of 1:10,000. On June 7 he gave a 1 plus cutaneous reaction to coccidioidin in a dilution of 1:1,000.

Cover slip examination of sputum forwarded to Dr. Smith September 13 revealed a few double-contoured, endosporulating spherules. No tubercle bacilli were seen. Cultures and animal inoculations confirmed the presence of *C. immitis*.

Dr. Smith commented as follows on the results of serologic studies: "Complement fixation test: dilution of 1:2, 2 plus. Precipitin test: unsatisfactory. Because of the fatty character of the serum, the precipitin tests gave unsatisfactory results. The low titer of complement fixation and the questionable precipitin reaction are characteristic of quiescent coccidioidal infection associated with solitary cavity."

Serial roentgenograms taken during the patient's stay in the hospital revealed little change in the appearance of the cystlike cavity (fig. 4B). His temperature, pulse and respiration remained normal. On November 7 iodized poppyseed oil introduced directly into the main primary bronchus through a ureteral catheter failed to fill any defects in the area of the cavity. Apparently there was no sufficiently large bronchial communication, as the bronchial tree itself was well outlined and showed no evidence of pathologic change. He was discharged on November 30, with a diagnosis of latent coccidioidal cavitation.

On Jan. 21, 1941, he stated that he had been entirely well after returning home. Sputum was present only occasionally and in slight amounts. Roentgen examination revealed the persistence of the cystlike cavity in the left infraclavicular area, with little evidence of surrounding reaction.

He was last seen on September 16, at which time he felt entirely well and had been working in the fields. The cavity could no longer be outlined either by fluoroscopic or by roentgenographic examination. It had closed spontaneously, leaving only a small area of fibrosis.

A typical latent coccidioidal cavity was discovered during a routine examination of contacts with a patient known to have tuberculosis. The reactions both to coccidioidin and to tuberculin were positive. The importance of distinguishing between the two types of cavitation is apparent. The patient was kept under roentgenographic observation for eighteen months; final closure of the cavity occurred under normal living and working conditions.

CASE 5.—C. H., a 28 year old married white American service station worker, had been a resident of Kings County (San Joaquin Valley) for ten years.

First Admission (April 28 to May 15, 1939).—The patient had been referred to the clinic at Springville by his local physician because of frequent blood spitting for approximately two years. Four days before examination he had raised about 1 ounce (30 cc.) of red blood in association with a severe attack of coughing. Otherwise, he felt well and did not complain of weakness, loss of strength or easy tiring. There was no history of chronic cough or expectoration, although the patient stated that occasionally he coughed and raised "some" sputum. No history of thoracic pain or unexplained fever was elicited.

Past History: The patient had had the usual childhood diseases. He had not had any recent attacks of influenza or severe infections of the respiratory tract. No history of erythema nodosum or erythema multiforme was obtained.

Family History: The patient's mother died at the age of about 35 of tuberculosis following childbirth. At this time he was ten years old. There was no other history of tuberculosis in the family.

Physical Examination: The patient was well nourished and appeared to be in good health. The chest was entirely normal. Studies of the blood revealed that the

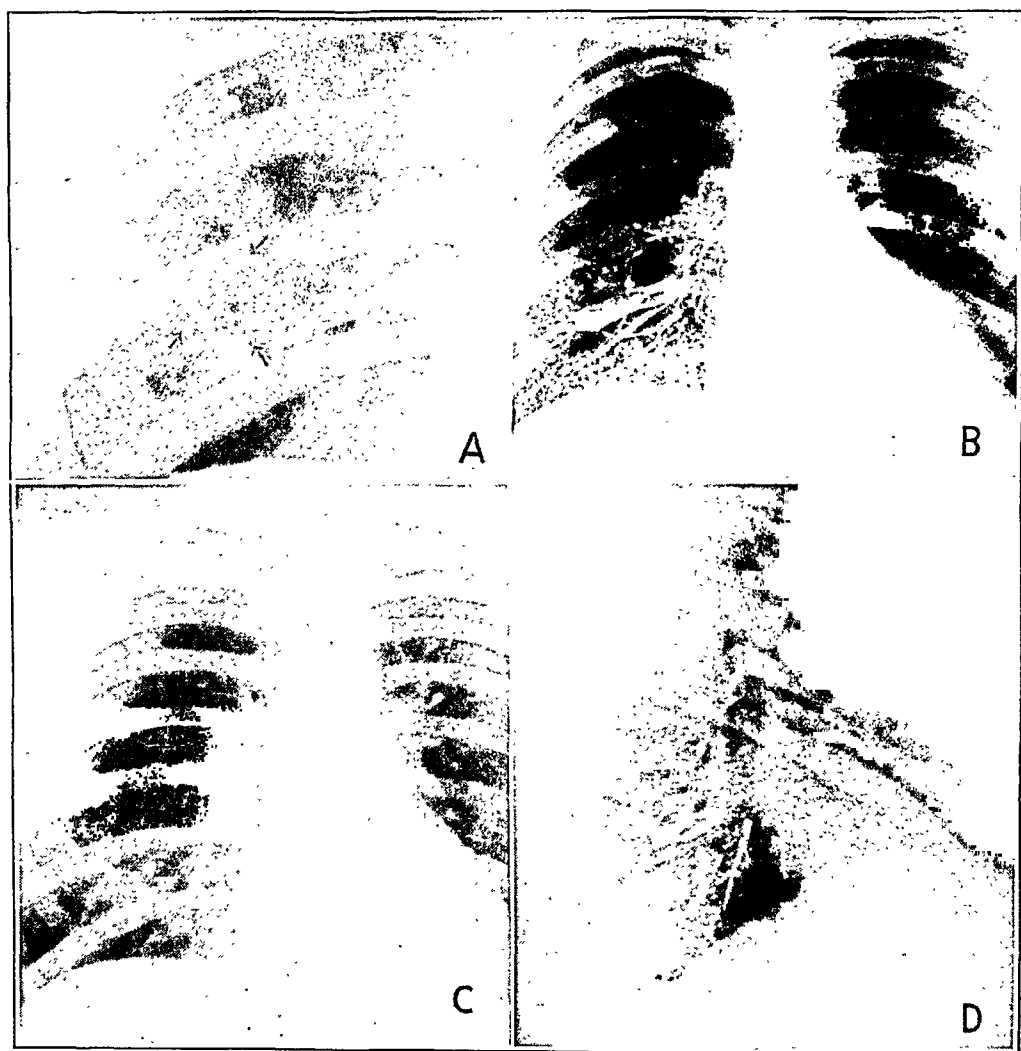


Fig. 5.—Case 5 (C. H.). Roentgenograms taken (A) April 19, 1939, (B and C) May 11, 1939 and (D) Feb. 3, 1941.

sedimentation (Brooks) was normal, the Kline reaction negative, the hemoglobin content 16.5 Gm. per hundred cubic centimeters, the red cell count 5,120,000 and the white cell count 7,100, with 74 per cent neutrophils, 25 per cent lymphocytes and 1 per cent eosinophils. During the patient's entire stay in the hospital there was no elevation of temperature or abnormality of pulse or respiration.

Course of Illness: Roentgenograms (fig. 5 A) taken April 19 in the outpatient department had been interpreted as follows: "A thin-walled cavity in the right

pulmonary field beneath the fourth interspace measures approximately 3.5 cm. in diameter. The pulmonary fields are comparatively clear aside from a slight amount of peribronchial haziness adjacent to the descending right bronchial tree. In a right lateral view the same annular shadow appears in the lower lobe posterior to the root of the lung."

Shortly after admission blood-tinged sputum was obtained and was found negative for tubercle bacilli. The cutaneous reaction to old tuberculin in a dilution of 1:10,000 was 1 plus and to coccidioidin in a dilution of 1:10 was 3 plus. On May 12, 2 guinea pigs were inoculated with digested and concentrated sputum. Neither gave any evidence of a pathologic condition when killed six and eight weeks later, respectively. Just before death both gave negative reactions to 0.1 of old tuberculin in a dilution of 1:100.

Bronchoscopic examination on May 11 failed to reveal pathologic changes in the larynx, trachea or primary bronchial tree. A smear of material obtained direct from the bronchus was negative for tubercle bacilli. With the patient under fluoroscopic observation, iodized poppyseed oil introduced into the lower lobe of the right lung through a ureter catheter outlined the bronchial tree and then pooled in the bottom of the cavity (fig. 5 B). The structure communicated with a fairly large bronchial branch, and this connection could be visualized easily in the lateral view with the patient in the vertical position (fig. 5 C). There was no evidence of other pathologic change in the bronchial tree.

The patient was discharged from the hospital with a diagnosis of a latent pulmonary coccidioidal cavity, without evidence of pulmonary tuberculosis. He was advised to refrain from work for several months.

Ten months later he stated that he had been working in a service station since the previous August and had been in good health. "Occasional color" had been noted in small amounts of sputum raised after severe physical effort. The roentgenographic appearance of the cystlike cavity was unchanged. He was advised to continue with his work.

He was next seen on Oct. 23, 1940, when he stated that two weeks previously a heavy truck tire, which he had been changing, had slipped off the wheel and struck him heavily on the chest. Two hours later he had had a sudden hemorrhage in association with severe coughing, and had raised approximately a half cupful of bright red blood. The hemorrhage had continued throughout the next few days, with the amount of bleeding gradually subsiding and the blood becoming darker. There had been no associated fever, chills or thoracic pain. He had returned to Springville on the advice of his physician. The roentgenographic appearance of the cavity in the base of the right lung was little changed at this time. A specimen of sputum obtained during the few days following this visit to the clinic and examined both by direct smear and by concentration was negative for tubercle bacilli. Petragani's medium inoculated with sputum failed to yield any growth after four months. During two hours of observation the sedimentation curve (Cutler) of the blood was normal, or quiescent. *C. immitis* was isolated by culture and by animal inoculation, with both mycelial growth and spherules, from a specimen of sputum obtained October 25. *Mycobacterium tuberculosis* was not isolated.

The patient was advised to refrain from all work for three months and to follow a regimen of rest. On Jan. 10, 1941, when he reported to the outpatient department, he stated that small pulmonary hemorrhages had occurred after any severe exertion. He had experienced the last one, ten days previous to examination, after carrying a heavy tub of water into the back yard. This effort had

been followed by a coughing spell, and the sputum had contained considerable red blood. In roentgenographic appearance the cavity in the base of the right lung was approximately unchanged in size and shape. Because of the continued bleeding the patient was advised to return to the hospital for institution of pneumothorax.

Second Admission (Jan. 27 to Feb. 24, 1941).—He was placed on a regimen of modified rest in bed and initial pneumothorax was established on the right side on January 30. During the stay in the ward he was noted to have occasional slight cough productive of less than 1 drachm (3.7 cc.) of slightly mucoid sputum every twelve hours. Definite double-contoured spherules, resembling *C. immitis*, were demonstrated in a moist preparation of sputum examined January 29. No tubercle bacilli could be observed in preparations treated with acid-fast stain. Dr. Smith commented as follows on a specimen of blood serum: "There were no demonstrable precipitins. Complement fixation was complete in the first tube (dilution of 1:2) and partial in the second tube (dilution of 1:4); it was clear thereafter."

After establishment of pneumothorax therapy the patient was discharged from the hospital. The cystlike cavity appeared to be closing (fig. 5D).

On May 21 he stated that he had been generally well. A small amount of bloody sputum had been expectorated for two days of the preceding week. Pneumothorax refills were continued twice a week in order to obtain an effective collapse. Fluoroscopic examination revealed moderate expansion of the lung and the continued presence but reduced size of the cavity.

At his last examination, on September 8, he appeared well. Roentgen examination disclosed a good collapse on the right side. The previously described cavity in the base of the right lung could no longer be visualized.

In this case of latent coccidioidal cavity of the lung, pneumothorax therapy was given because of the history of frequent hemoptyses. The patient could not retain employment because of these episodes, which had been witnessed by his employer. The cavity had an open bronchial communication, and therefore collapse therapy was effective, as indicated by the last roentgenogram. The robust, healthy appearance of the patient since the time of his first examination, despite the cavity and the hemoptyses, is worthy of note. Over two years' roentgenographic observation the cavity did not change, nor was there any tendency for the infection to disseminate, despite the frequent and considerable pulmonary bleeding. Digestion of the sputum in May 1939 by sodium hydroxide, the customary procedure previous to concentration, destroyed any spherules present and prevented isolation of the fungus. Alkaline digestants rapidly dissolve the endospores. In October *C. immitis* was found by Dr. Smith in sputum which had not been previously treated with sodium hydroxide. The cavity has apparently been closed by pneumothorax.

CASE 6.—W. B., a 36 year old married American farm laborer, was born in Texas and had resided in Kings County (San Joaquin Valley) for five years.

First Admission (Nov. 15, 1940 to Jan. 28, 1941).—The patient had been referred by his physician to the chest clinic because of a slightly productive chronic cough of one year's duration. At times he had noticed some streaks of blood in the sputum

and pain, which was variable and was aggravated by deep breathing, both on the left and on the right side of the chest. He had lost strength, and his weight had decreased from 170 to 155 pounds (77.1 to 70.3 Kg.) in the last year. On closer questioning he stated that he might have had a slight cough for a number of years.

- Past History: No history of valley fever, erythema nodosum or other cutaneous rash could be elicited. The patient had had no definite exposure to tuberculosis, although 1 sister, who died at the age of 33, was suspected of being "tuberculous."

Physical Examination: The patient was a large well developed, swarthy man who did not appear ill. His skin was somewhat loose, suggesting recent loss of weight. The chest appeared symmetric and expanded well and equally on the two sides. The only definite abnormality was a slight increase in the spoken

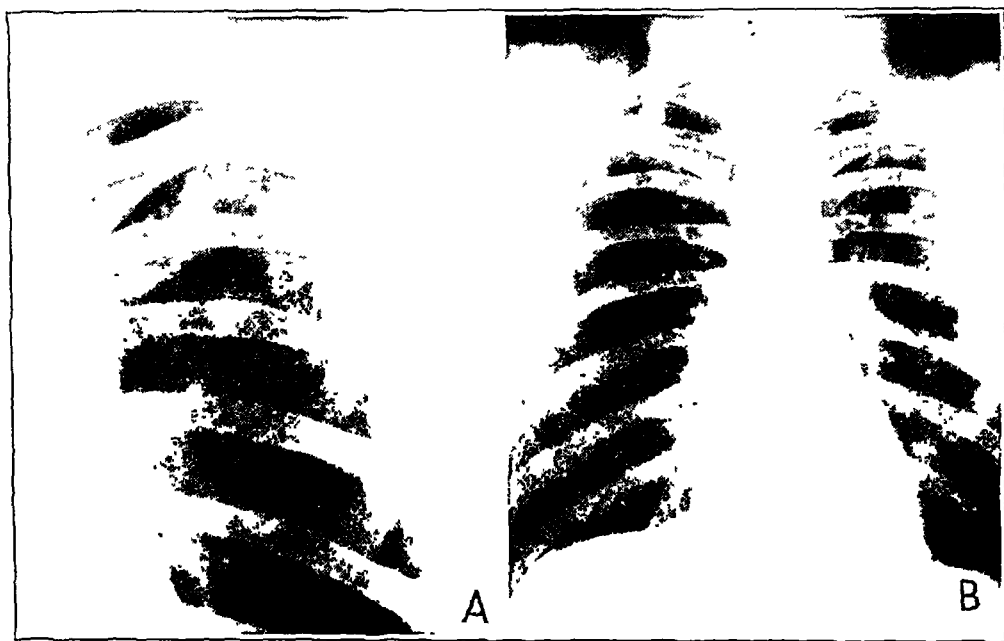


Fig. 6.—Case 6 (W. B.). Roentgenograms taken (A) Nov. 6, 1940 and (B) April 8, 1941.

voice over the left axilla. Studies of the blood yielded the following data: red cell count 4,460,000, white cell count 9,800, with 58 per cent neutrophils, 32 per cent lymphocytes, 7 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils, hemoglobin concentration (Tallqvist) 85 per cent red cells and platelets normal. The Kline reaction of the blood was negative.

Roentgen examination in the outpatient department on November 6 disclosed a thin-walled cavity, measuring approximately 4 by 5 cm., beneath the left infra-clavicular area and near the periphery of the lung (fig. 6A). There was a slight amount of surrounding reaction, and increased markings extended outward from the hilus toward the cavity. The pleura in the right costophrenic angle and an interlobar septum in the middle of the right pulmonary field were thickened. The clinical impression was that of a latent coccidioidal cavity of the lung.

Course of Illness: The patient was permitted restricted physical activity and given a high caloric diet. His temperature, pulse rate and respiratory rate remained within normal limits.

A specimen of sputum collected on November 6 was reported two months later by Dr. Smith to be positive for *C. immitis* and negative for *Myco. tuberculosis*. Mycelial growth had been demonstrated in cultures, spherules in inoculated animals and mycelial growth in cultures of tissues from these animals.

Cutaneous reactions to tests, made November 16, were as follows: coccidioidin (1:1,000), 1 plus; coccidioidin control, negative, and old tuberculin (1:100,000), 1 plus. Two specimens of sputum collected over seventy-two hours and concentrated and 1 specimen sent to the state laboratory were negative for tubercle bacilli. Cultures planted on Petragani's medium were negative for growth.

The report of the serologic studies ran as follows: "Complement fixation test: dilution of 1:2, 3 plus, and dilution of 1:4, 1 plus. Precipitin test: undiluted, negative. The low titer of complement fixation and the questionable precipitin reaction without evidence of active infection are characteristic of the quiescent coccidioidal infection associated with solitary cavity."

On November 19 a roentgenogram taken in the left lateral view disclosed the previously described cavity in the upper lobe of the left lung, posterior to the hilus. Roentgen examination on Jan. 25, 1941, shortly before the patient's dismissal from the hospital, revealed the thin-walled cavity in the left infra-clavicular area. The cavity was somewhat smaller than it had appeared in the original roentgenogram, and there was less surrounding reaction. Elsewhere the pulmonary fields remained perfectly clear.

On discharge from the hospital the patient had gained 24 pounds (10.9 Kg.) in weight and looked generally improved. He was advised to return to his former occupation.

Follow-Up Observation.—On April 8 he returned to the clinic. He stated that he had had three "colds," associated with slightly productive cough, at different times since dismissal from the hospital. Otherwise he felt well and intended to work. A specimen of sputum sent to Dr. Smith on February 6 by the patient, during a "cold," was found to contain a few viable organisms of *C. immitis*. Roentgen examination on April 8 showed little change in the appearance of the cavity (fig. 6B). A slight amount of peripheral collateral reaction remained, but the pulmonary fields elsewhere were clear.

The patient was last seen on September 20. He had been working in the cotton fields. He felt quite well but complained of two "colds" since the previous examination, associated with the production of 0.5 ounce (15 cc.) of occasionally blood-streaked sputum per day. He also had been bothered with some pain on the left side of the chest related to respiration. Roentgenographic examination of the chest showed that the cavity was unchanged in size, with a small amount of persistent surrounding reaction. Elsewhere the pulmonary fields remained clear.

In this case the catarrhal symptoms, with a more or less chronic productive cough and frequent "chest colds," are predominant. Occasionally the sputum was blood streaked. Despite the presence of pulmonary cavitation and occasional spherule-laden sputum, this man has continued hard physical labor for seven months without ill effect.

CASE 7.—J. C. S., a 27 year old white married American farm worker, had resided in Tulare County (Earlimart) for three years.

Admission to Hospital (May 26 to June 29, 1941).—Two years prior to admission the patient had had an attack of "pleurisy" with severe pain beneath the left shoulder blade not definitely related to respiration.

One year ago he had suffered from "influenza," associated with a slightly productive cough, chills and general malaise. One and a half days after his recovery he had begun to cough up bloody sputum during heavy labor. He had stopped work and gone home to bed. The next morning, during severe coughing, he had raised "about a handful of red blood." This bleeding had continued for a week in gradually decreasing amounts, and the blood had become darker, until it disappeared. Roentgen examination by his local physician had revealed nothing abnormal. Since then the patient had had frequent slight hacking cough, aggravated by such factors as hay dust and exertion.

His general health had remained good, and he had been able to work until four weeks prior to admission, when he had again suffered a mild attack of "influenza," associated with fever, a productive cough, general malaise and aggravation of his thoracic pain. He had remained at home only a few days and then returned to his work as a cotton chopper. About this time he had begun to spit up a small amount of blood every morning, which on some occasions amounted to several mouthfuls. He had continued his work despite the blood spitting and



Fig. 7.—Case 7 (J. C. S.). Roentgenograms taken (A) May 21 and (B) June 16, 1941.

felt fairly well. He had been referred to Springville by State Relief Administration authorities.

Past History: No history of erythema nodosum or erythema multiforme was elicited. One brother had been tuberculous ten years previous but had made a complete recovery; possibly the patient had been exposed to this brother during his illness.

Physical Examination: The patient was rather thin but apparently was healthy. Examination of the chest revealed nothing definitely abnormal.

Studies of the blood yielded the following data: hemoglobin content 16 Gm. per hundred cubic centimeters (94 per cent Sahli), red cell count 4,730,000, white cell count 5,150, with 3 per cent band neutrophils, 71 per cent mature neutrophils, 23 per cent lymphocytes and 3 per cent monocytes, Kline reaction negative and sedimentation curve and rate (Brooks and Cutler) normal.

Roentgen examination during his first visit to the clinic, on May 21, disclosed a thin-walled cavity with little surrounding reaction, measuring approximately 3 cm. in diameter and lying beneath the fourth interspace on the left side (fig. 7 A).

Calcified foci were noted in the right pulmonary field. The clinical impression was latent coccidioidal pulmonary cavitation.

Course of Illness: The patient was placed on a regimen of modified rest in bed. He had an occasional slightly productive cough, with sputum amounting to 2 to 3 drachms (7 to 12 cc.) daily. His pulse rate varied from 64 to 98 beats per minute, and the temperature was occasionally elevated to 99 F. On the day of admission the patient gave cutaneous reactions of 1 plus and 2 plus, respectively, to old tuberculin in a dilution of 1:100,000 and coccidioidin in a dilution of 1:1,000. Many specimens of sputum collected over varying periods and concentrated were examined both by smear and by culture and were negative for tubercle bacilli. Two weeks after admission a few organisms with doubly refractile walls resembling the spherules of *C. immitis* were noted in a moist preparation of sputum. A few small white colonies, also typical of *C. immitis*, were produced on Sabouraud's medium inoculated with this sputum.

A second roentgen examination, ten days after the first, revealed no change in the appearance or size of the previously described cavity. In the lateral view the cavity lay slightly below and posterior to the hilus, in the upper portion of the lower lobe (fig. 7 B).

A specimen of sputum forwarded to Dr. Smith on June 4 was reported positive for *C. immitis*. Cultures and animal inoculations confirmed this report.

Both complement fixation and precipitin tests were negative.

The last roentgen examination, made on September 27, showed the cavity in the base of the left lung was unchanged in size, shape and appearance. A small amount of reaction in relation to the bronchial tree remained immediately adjacent to the cavity. A specimen of sputum forwarded to Dr. Smith a few days later was reported to contain viable *C. immitis*. A few weeks previously the patient had returned to his work as a laborer and had remained generally well.

Pleurisy of two years' duration was marked at the beginning of the second year by an acute episode of what was termed "influenza" but in all probability was primary coccidioidomycosis. This episode was accompanied by hemoptysis, which occurred again one month prior to admission, appearing at daily intervals. The roentgenographic observation of a typical solitary cavity was followed by the demonstration of *C. immitis* in the sputum. The negative serologic reactions can be disregarded in view of similar negative reports in 2 cases (8 and 9) of known coccidioidal infection.

CASE 8.—E. J. T., a 30 year old Texas-born white housewife, had resided in Tulare County (San Joaquin Valley) for four years.

Admission to Hospital (April 18 to June 28).—The patient had been in good health until a fortnight before admission, when symptoms of "flu" had developed, with chills, generalized aching pains, malaise and a slightly productive cough. She had remained in bed two days and then, feeling quite well, had resumed her household activities. Approximately ten days later, while ironing clothes, she had suddenly begun to spit up blood. The slight cough associated with the bleeding had lasted for about a half-hour, during which time the patient lost about 2 ounces (60 cc.) of blood. Her physician had advised examination at the hospital in Springville.

She had since been symptom free except for a slightly productive, persistent cough, unassociated with further bleeding.

Past History: No relevant history could be elicited. The patient had not had erythema nodosum or erythema multiforme, had not noticed any loss of weight, strength or physical endurance and had no knowledge of a family history of tuberculosis or of contact with a tuberculous person.

Physical Examination: The patient was well developed and nourished and did not seem ill.

Examination of the chest revealed nothing definitely abnormal.

Course of Illness: The patient was placed on a regimen of modified rest in bed. There was no elevation of pulse rate, temperature or respiratory rate. Examination of the blood revealed the hemoglobin content was 13.5 Gm. per hundred cubic centimeters (79 per cent Sahli), the red cell count 4,500,000 and the white cell count 19,500, with 4 per cent band neutrophils, 70 per cent mature neutrophils,

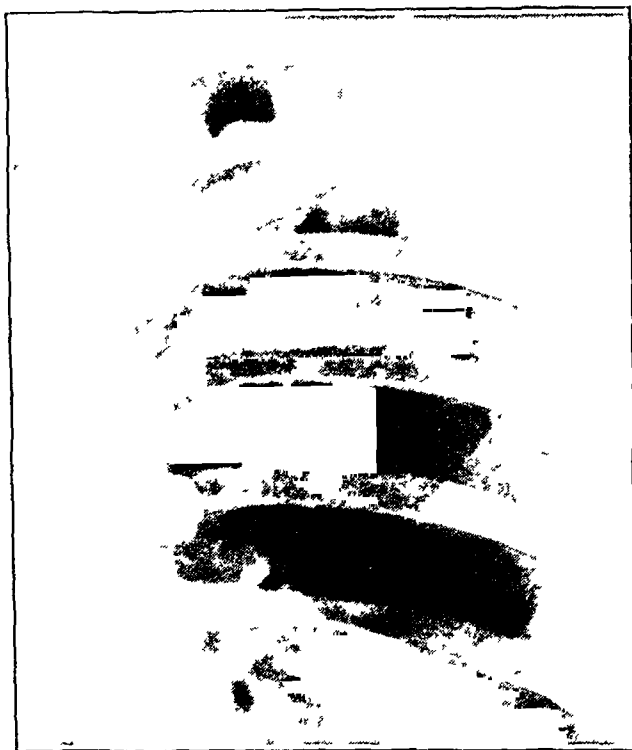


Fig. 8.—Case 8 (E. J. T.). Roentgenogram taken April 16, 1941.

21 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The appearance of the red cells was normal. About two weeks after admission the red cells were still normal, and the white cell count was 10,250, with 1 per cent band neutrophils, 72 per cent mature neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The sedimentation rate (Brooks) of the blood was 6 mm. at the end of sixty minutes, and the curve was considered to be normal. Coccidioidin in a dilution of 1:1,000 produced a 1 plus cutaneous reaction, and old tuberculin in a dilution of 1:100 produced a 2 plus cutaneous reaction. The Kline reaction of the blood was negative. She had only a slightly productive cough, and sputum was rather difficult to obtain. Twenty-four to forty-eight hour specimens were collected and concentrated. Neither examination nor culture revealed tubercle bacilli.

A roentgenogram of the chest taken at the clinic prior to admission disclosed in the outer first interspace on the left side a small soft area of infiltration, within which was a cavity approximately 1.5 cm. in diameter (fig. 8). Else-

where the pulmonary fields were comparatively clear. Comparison of this roentgenogram with one taken a week earlier by the patient's local physician disclosed some decrease in the size of the area of infiltration but no evidence of cavitation. The clinical impression was subsiding acute primary coccidioidomycosis, with pulmonary cavitation.

On June 5 Dr. Smith reported that of three specimens of sputum forwarded to him on April 21, April 25 and May 12, the second and third contained *C. immitis* but were negative for *Myco. tuberculosis*. These results were confirmed by routine cultural and animal inoculation studies.

Roentgen examination on April 29 showed little change in the appearance of the lesion or the surrounding reaction in the apex of the left lung. Elsewhere the pulmonary fields were clear. The only change revealed by roentgen examination a month later was some decrease in the surrounding reaction.

The patient was allowed to resume physical activity slowly and was discharged to her home seventy-four days after admission, with the advice to return to her ordinary household duties.

The serologic reactions were completely negative.

When she was last seen in the clinic, on August 9, she felt well. Two weeks before she had "spit a small amount of blood." Roentgen and fluoroscopic examination revealed the cavity was still present, little changed in size or appearance since its discovery four months previously.

This case, with a history of an acute illness suggestive of primary coccidioidomycosis and the appearance of cavitation in the apex of the left lung approximately two weeks later, at about the time of the hemoptysis, illustrates, as does case 11, the association of cavitation with primary disease. The negative serologic reactions may be disregarded in view of the isolation of *C. immitis* from the sputum.

CASE 9.—S. B., a 35 year old married American truck driver, was born in Colorado and had been a resident of Fresno and Kings counties (San Joaquin Valley) for fourteen years.

Admission to Hospital (May 29 to June 10, 1941).—In January 1941 the patient had a severe attack of "influenza" and had been in bed for five days, with severe cough, fever and general malaise. The cough had persisted for several weeks. He had then remained in good health until the middle of April, six weeks prior to admission, when one day, after clearing his throat, he expectorated a small amount of red blood. Similar small hemoptyses then occurred daily; they were not particularly related to physical activity. His work was heavy and necessitated driving a large truck. There had been no respiratory symptoms previous to these episodes of bleeding. For months his longest period without hemoptysis was only two days. He had not felt it necessary to consult a physician and had continued with his work of hauling rock. On May 17, after considerable physical effort, he had suddenly raised about two mouthfuls of bright red blood, an amount definitely greater than any previous one. This frightened him, and he consulted a physician, who referred him to the hospital at Springville, after a roentgen examination of his chest. Until admission he had remained in bed at home and had had no further hemoptyses. There were no other complaints and no loss of weight, strength or physical endurance.

Past History: No history of erythema nodosum, erythema multiforme, valley fever, familial tuberculosis or contact with a tuberculous person could be elicited.

Physical Examination: The patient appeared well nourished and healthy. Examination of the chest disclosed nothing abnormal. The temperature, pulse rate and respiratory rate remained within normal limits during the entire period of hospitalization. Studies of the blood yielded the following data: red cell count 5,300,000, white cell count 9,400, with 63 per cent neutrophils, 19 per cent lymphocytes, 15 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils and hemoglobin content 16 Gm. per hundred cubic centimeters. The red cells appeared normal, the Kline reaction was negative and the sedimentation rate (Cutler) was 11 mm. in sixty minutes.

Course of Illness: The patient was placed on a regimen of modified rest in bed. The cutaneous reactions to coccidioidin (1:100) and old tuberculin (1:100) were 3 plus and negative, respectively.

Numerous examinations of sputum, carried out by direct and concentration methods, including cultures and guinea pig inoculations, failed to reveal tubercle



Fig. 9.—Case 9 (S. B.). Roentgenograms taken (A) May 29, and (B) June 5, 1941.

bacilli. On May 31 several round refractile bodies, slightly larger than lymphocytes and resembling *C. immitis*, were present in the sputum.

On June 23 Dr. Smith reported that specimens of sputum received on June 2 and 4 were positive for *C. immitis*. Cultures and animal inoculations had been fully confirmative.

Roentgen examination on May 29 revealed a thin-walled, somewhat elongated cavity, measuring approximately 2 by 4 cm., beneath the third rib on the left side (fig. 9 A). There was practically no surrounding reaction, and the cavity had a more or less "punched out" appearance. Elsewhere the pulmonary fields were clear. The clinical impression was latent coccidioidal pulmonary cavitation.

About a week later a left lateral view of the chest revealed the thin-walled cavity to be in the upper portion of the lower lobe of the lung, posterior to the root, overlying the middle thoracic portion of the spine and roughly ovoid (fig. 9 B).

During the stay in the hospital there was no further evidence of hemoptysis, and the patient was discharged to his home. The results of the complement fixation and precipitin tests were negative.

One month after discharge the patient stated that he felt well and had not had cough or pulmonary bleeding. The roentgenographic appearance of the cavity was unchanged.

Repeated hemoptyses finally drew attention to a latent coccidioidal cavity. Despite a long period of pulmonary bleeding the patient continued his work, without reactivation or dissemination of the disease. In this case, as in case 5, physical exertion tended to aggravate the bleeding and forced the patient to stop work temporarily. The negative serologic reactions must be disregarded.

CASE 10.—C. C. G., an 11 year old American-born school girl of Mexican parentage, had resided in Tulare since birth.



Fig. 10.—Case 10 (C. C. G.). Roentgenogram taken June 14, 1941.

Admission to Hospital (May 12, 1941).—The patient was first seen in the outpatient department on April 5, where she was brought by her mother because of persistent cough and expectoration following a severe "cold" of about three weeks' duration and failure to gain in weight. There had also been slight exposure to an aunt who had tuberculosis. The temperature was 98.4 F. and the pulse rate 100 per minute.

Fluoroscopic examination revealed a large annular shadow in the apex of the left lung, adjacent to the mediastinum. It was necessary to rotate the child to bring the cavity into view. The cavity was poorly visible in a roentgenogram taken with the child in the usual posteroanterior position. The pulmonary fields were otherwise clear.

A month later the "cold" had improved and the child felt much better. The cavity in the left apex was still fluoroscopically visible. A roentgenogram disclosed the cavity beneath the sternal end of the first rib on the left side, lying close to the mediastinum and measuring approximately 2 by 3 cm. Although it had a fairly thick wall, there was little surrounding parenchymal reaction. Elsewhere the

pulmonary fields were comparatively clear. The mother was advised to permit the child to be hospitalized for study and observation.

Past History: No history of erythema nodosum or erythema multiforme could be elicited, and otherwise the history was irrelevant.

Physical Examination: On the day of admission to the children's convalescent unit, the child was rather thin, but she was not ill. No abnormal chest signs could be elicited. At the time of the first examination, a month before, rather marked whispering pectoriloquy had been observed in the apex of the left lung and in the left axilla and at the lower border of the left scapula.

Course of Observation: The child was permitted to resume full physical activity after the preliminary routine isolation. There was no elevation of temperature, pulse rate or respiratory rate. The cough had stopped, and sputum was completely absent. Studies of the blood revealed that the Kline reaction was negative, the hemoglobin concentration 16 Gm. per hundred cubic centimeters (91 per cent, Sahli), the red cell count 5,580,000 and the white cell count 6,200, with 1 per cent band neutrophils, 39 per cent mature neutrophils, 51 per cent lymphocytes and 9 per cent monocytes. The appearance of the red cells was normal and the sedimentation rate (Brooks) 4 mm., with a normal curve. The cutaneous reaction to coccidioidin (1:100) was 1 plus, and the cutaneous reactions to old tuberculin (1:100) and purified protein derivative (second strength) were negative. Three specimens of material obtained by gastric lavage were concentrated and examined for tubercle bacilli, both directly and by culture. A portion of each was sent to Dr. Smith. On May 18 specimens of blood serum were forwarded to Dr. Smith for serologic tests. His report on June 6 was as follows: "Complement fixation test: dilution of 1:2, 3 plus; dilution of 1:4, 1 plus, and dilution of 1:8, negative. Precipitin test: undiluted, 3 plus; dilution of 1:10, 1 plus, and dilution of 1:40, negative. The positive result of the complement fixation test and the moderately positive result of the precipitin test are characteristic of the serologic reactions associated with arrested solitary cavity due to *C. immitis*."

Roentgen examination on June 14 with the child in an oblique anteroposterior position revealed that the previously described cavity had decreased somewhat in size and there was little surrounding reaction (fig. 10). Elsewhere the pulmonary fields remained clear.

At the date of this report (September 18) it has not been possible to recover *C. immitis* from the gastric contents. The diagnosis of latent primary coccidioidal infection, with pulmonary cavitation, is based on a positive cutaneous reaction to coccidioidin and negative cutaneous reactions to old tuberculin (1:100) and purified protein derivative (second strength). The positive reaction to the complement fixation test was of sufficiently high titer to be significant. Other presumptive evidence is furnished by the typical roentgenographic appearance of the solitary apical cavity and by the clinical history. Actual recovery and isolation of the fungus may have to await the return of an acute episode of respiratory infection, with associated production of sputum. Specimens of sputum obtained in the clinic when the child was first seen were examined in the routine manner for tubercle bacilli only and were negative for these organisms.

CASE 11.—This case is an instance of acute primary coccidioidomycosis, in which it was possible to observe roentgenographically the development of typical pulmonary disease, including the appearance and, three months later, the closure of a solitary apical cavity.

A. P., a 29 year old single Portuguese dairy worker, had resided in Tulare for two years.

Admission to Hospital (Feb. 21 to Aug. 17, 1941).—He was first seen in the outpatient department on Feb. 4, 1941. For the two years previous he had felt

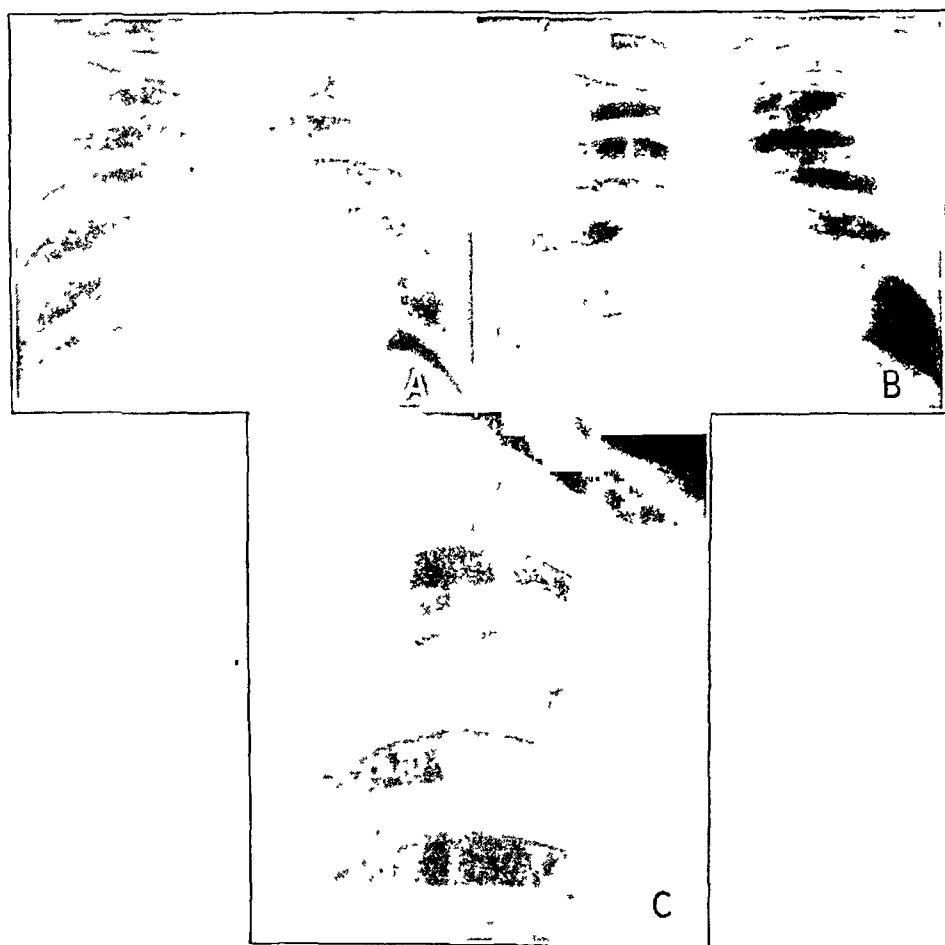


Fig. 11.—Case 11 (A. P.). Roentgenograms taken (A) February 4 and (B, C.) April 22, 1941.

unwell at times and had noted occasional sharp pain on the left side of the chest, associated with some shortness of breath when he lay on his left side. In November 1940 he had contracted what he thought was a "cold." It had persisted and was associated with severe coughing, expectoration of considerable yellowish sputum, night sweats and occasional hoarseness. Because of these symptoms he had consulted a local physician, who told him after roentgen examination of his chest that he had pulmonary tuberculosis. He believed he had lost 5 to 6 pounds (2.3 to 2.7 Kg.) in weight. However, he had not lost any strength or had hemoptysis and had carried on his work in the dairy.

Past History: The patient had had a severe "cold" of six weeks' duration in 1935, with a productive cough and loss of weight and strength. No history of erythema nodosum, valley fever, tuberculosis in the family or contact with a tuberculous person could be elicited.

Physical Examination: The patient was well developed and muscular and did not appear ill. Slight hoarseness was present, but indirect laryngeal examination failed to disclose any definite pathologic condition. The expansion of the chest was decreased on the left side. Harsh breath sounds were noted at the lower border of the left scapula and in the left axilla, with whispering pectoriloquy at the lower border and just beneath the angle of the left scapula. No rales were heard.

Roentgen examination revealed soft exudative infiltration scattered throughout the left pulmonary field, of fairly marked density in the apex (fig. 11 *A*). The right pulmonary field was relatively clear of infiltration, although there was perihilar haziness. The clinical impression was acute primary coccidioidomycosis.

Course of Illness: The patient was confined to bed. There was no elevation of the temperature, pulse rate or respiratory rate. Two to 3 drachms (7 to 11 cc.) of slightly purulent sputum was raised every twenty-four hours. Studies of the blood yielded the following data: hemoglobin content 17 Gm. per hundred cubic centimeters (100 per cent Sahli), red cell count 5,250,000, white cell count 10,350, with 47 per cent neutrophils, 40 per cent lymphocytes, 9 per cent monocytes and 4 per cent eosinophils, appearance of red cells normal and Kline reaction negative. The following cutaneous reactions were obtained: coccidioidin (1:1,000), 3 plus; coccidioidin control, negative, and old tuberculin (1:10,000), 1 plus. On repeated occasions sputum examined by direct, concentration and culture methods was negative for tubercle bacilli, as was material obtained by gastric lavage and concentrated. Two specimens of sputum taken on March 27 and April 3 were sent to Dr. Smith, who reported on May 10 that both contained viable *C. immitis*, demonstrated by culture and animal inoculation. On April 23 the sedimentation rate (Brooks) of the blood was 17 per cent at the end of sixty minutes and the resultant curve was interpreted as slightly pathologic.

Blood serum preserved with merthiolate was sent to Dr. Smith, who reported on April 12 as follows: "Complement fixation test: dilution of 1:2, 4 plus, and dilution of 1:4, 1 plus. Precipitin test: undiluted and dilution of 1:10, 1 plus. These results check each other and indicate the mild type of serologic response associated with primary infection which is subsiding or with a solitary cavity, such as has been observed in your patients. The results would not be incompatible with cavity formation, which you believe is occurring."

On March 13 the patient was allowed to resume some physical activity. Roentgen examination of the chest on March 21 disclosed clearing of some of the previously described patchy infiltration on the left side. There remained three rather distinct nodular shadows, one just outside the right hilus and the other two in the left pulmonary field. In the apex of the left lung there was an area of partial atelectasis and within it a rounded area of increased radiability, suggestive of early cavitations.

Apparently the cavity was forming during the active primary infection, and on April 22 roentgen examination of the chest and of the apex of the left lung revealed a definite cavity, measuring approximately 2 cm. in diameter and possessing the thin, "ragged" walls characteristic of a newly formed cavity (fig. 11, *B* and *C*).

The patient continued to improve and was permitted more physical activity. He ceased raising sputum and consistently gained in weight. Roentgen examination

showed the persistence of several small circumscribed nodules outside the right hilus and the continued clearing of the previously described exudative reaction on the left side. The cavity remained; it had changed little in size but possessed the thin wall typical of a latent coccidioidal cavity.

Five weeks later roentgenograms disclosed that the infiltrate on the left had cleared further and that the cavity was no longer present but had apparently closed. Nodular infiltration persisted in the base of the left lung but had become more discrete. These observations were substantiated by fluoroscopic examination.

The patient felt well, was allowed unlimited exercise and had gained 18 pounds (8.2 Kg.) since his admission. There was no cough or production of sputum. He was discharged to his home six months after admission.

On October 15, roentgenographic study revealed persistence of two small nodules of infiltration beneath the first and the fourth interspaces on the left side. A small amount of fibrosis remained in the apex of the upper lobe on the left side, the cavity remaining closed. The patient felt "very well."

This case of active primary pulmonary coccidioidomycosis offered the unusual opportunity of watching the development of an associated solitary cavity in the apex of the left lung. The cavity developed despite healing of the general pulmonary infection. Clear evidence is furnished that such cavitation can be an accompanying feature of the primary infection. The cavity persisted for approximately three months and then closed spontaneously.

CASE 12.—This case is an instance of a large coccidioidal cavity associated with chronic symptoms and treated with pneumothorax, with approaching success.

J. C., a 33 year old Texas-born married ranch worker, had resided in Kings County (San Joaquin Valley) for twenty-three months.

Admission to Hospital (July 12, 1940 to Jan. 4, 1941).—In 1937 the patient had had a fairly severe attack of "pneumonia" followed by a chronic, productive cough, which in the year previous to admission had become so severe at times as to interfere seriously with his rest at night. Otherwise, he had felt well and had not lost weight or experienced undue fatigue. He had been able to carry on heavy farm labor with difficulty. He had not had thoracic pain or hemoptysis. Because of the chronic cough a roentgenogram (fig. 12 A) of the chest had been taken on May 21 during a survey by the State Bureau of Tuberculosis and forwarded to the hospital at Springville for interpretation, where a presumptive diagnosis of pulmonary tuberculosis had been made. When the patient first reported to the clinic at Springville, on July 3, another roentgenogram of the chest had disclosed the same large cavity lying outside the right hilus which had been visible in the first roentgenogram. There was a moderate amount of surrounding collateral reaction, and the hilus shadow appeared enlarged. Elsewhere the pulmonary fields remained comparatively clear. Hospitalization had been advised.

Past History: No definite history of valley fever, erythema nodosum, erythema multiforme or exposure to tuberculosis could be elicited.

Physical Examination: The patient was a moderately thin man, with an occasional loose cough, who did not appear ill. The chest was symmetric and expanded equally on the two sides. Resonance was slightly impaired over the right side of the chest anteriorly, and the breath sounds were somewhat louder at

the base of the right lung than at the base of the left one. No definite rales were noted. Studies of the blood revealed the red cell count was 4,340,000, the white cell count 11,550, with 59 per cent neutrophils, 34 per cent lymphocytes, 6 per cent eosinophils and 1 per cent monocytes and the hemoglobin content 15 Gm. per hundred cubic centimeters. The appearance of the red cells was normal.

Course of Illness: The patient was placed on a regimen of modified rest in bed. There were no abnormalities of temperature, pulse or respiration. Pneumothorax on the right side was started immediately because of the size of the cavity. Sputum, amounting to 1 drachm (3.7 cc.) of mucopurulent material during the first week of hospitalization, gradually decreased and completely disappeared at the end of four months.

A roentgenogram taken three weeks after admission with the patient in the right lateral position showed the cavity to be located in the upper portion of the lower lobe. It had become somewhat smaller. Roentgen examination one month

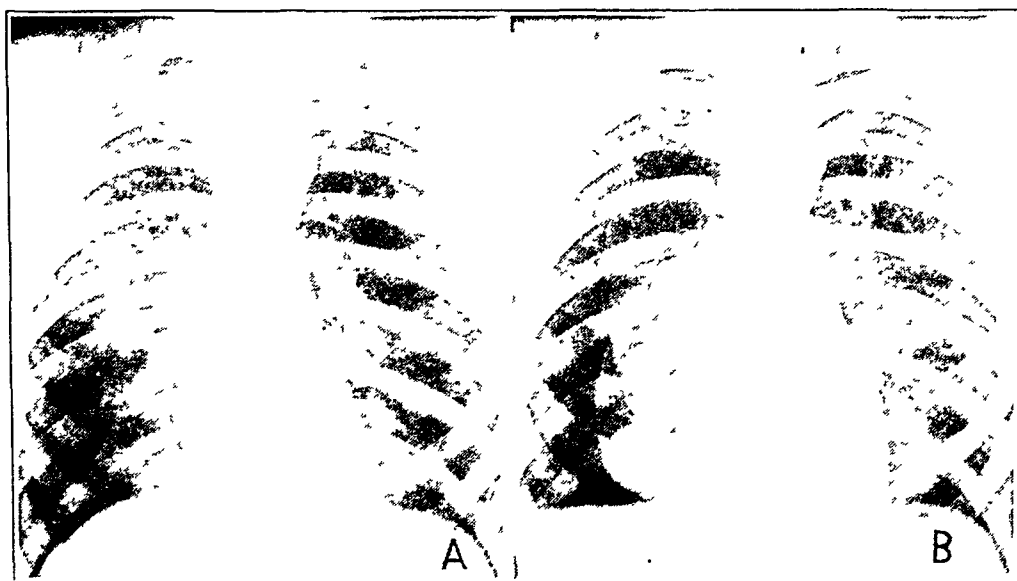


Fig. 12.—Case 12 (J. C.). Roentgenograms taken (A) May 21, 1940 and (B) June 20, 1941.

after admission with the patient in the posteroanterior position revealed that the pneumothorax on the right side had resulted in a moderate collapse of the lung and decrease in size of the cavity.

On numerous occasions the sputum was examined by direct smear, concentration and culture and was negative for tubercle bacilli. Moist preparations were negative for spherules of *C. immitis*.

A specimen of sputum referred to Dr. Smith on September 25 was positive for *C. immitis* and negative for *Myco. tuberculosis*, and the findings were confirmed by the usual culture and animal inoculation studies.

The following cutaneous reactions were observed: old tuberculin (1:100), negative; purified protein derivative (second strength), negative; coccidioidin (1:1,000), 1 plus, and coccidioidin control, negative.

Dr. Smith reported the following results of serologic tests made with blood serum prepared on November 28: "Complement fixation test: dilution of 1:2, 3 plus. Precipitin test: undiluted, 1 plus. The low titer of the complement fixation

and the questionable precipitin reaction are characteristic of serologic reactions in cases of quiescent coccidioidal infection with associated solitary cavity."

The patient's rapid improvement was manifested by a 15 pound (6.8 Kg.) gain in weight. He was allowed to resume exercise and was discharged to his home on Jan. 4, 1941, to return to the outpatient department for pneumothorax refills at intervals of two weeks. Roentgen examination of the chest shortly before his discharge revealed a good collapse on the right side and a decrease in the size of the cavity.

After discharge the patient remained at home on a regimen of restricted activity. Roentgenograms showed slightly more collapse on the right side and a small amount of fluid in the pleural space. He had occasional expectoration and cough but otherwise felt well. *C. immitis* was still present in sputum collected on March 16.

He continued to receive pneumothorax refills at intervals of two weeks. The last roentgenogram (fig. 12 *B*), taken on June 20, revealed a good collapse on the right side and a small amount of fluid in the pleural space. The cavity was much smaller, measuring about 1 cm. in diameter.

There has been little change in the roentgenographic appearance of the collapsed lung to date (September 18). The cavity is apparently closing. On July 24 355 cc. of turbid, straw-colored fluid was aspirated from the right pleural space. Bacteriologic studies of this fluid by Dr. Smith failed to yield any growth. Since then there has been no tendency for the fluid to reappear, and a satisfactory collapse has been maintained.

The appearance of the cavity, regardless of its large size, indicated a latent infection associated with chronic productive cough. Effectiveness of pneumothorax in closing the cavity cannot be completely evaluated at this date, although the decrease in size is promising. Spherule-laden sputum will probably remain until complete closure and healing are obtained.

CASE 13.—This case illustrates the occurrence of localized bronchiectatic change, rather than formation of a solitary cavity, due to coccidioidal infection, with the production of symptoms similar to those of cavitation. This case, first recorded in 1930, is the only one of this type encountered.

A. M. P., a 36 year old American widow, had resided in Tulare County (Dinuba and Visalia) for twenty-one years.

First Admission (Sept. 12 to Oct. 4, 1930).—The patient had been referred to the sanitarium because of a history of chronic cough of six months' duration and daily expectoration on the average of 0.5 ounce (15 cc.) of purulent sputum, which was frequently blood stained. She also complained of easy fatigability and loss of weight. Roentgen examination revealed a few changes in the apex of the right lung which were interpreted as infiltration with fibrosis, without definite evidence of cavitation (fig. 13 *A*). Moist rales were heard on several occasions over the upper lobe of the right lung. Many specimens of sputum were negative for tubercle bacilli. After one month's observation the patient was discharged, with a presumptive diagnosis of nontuberculous bronchiectasis.

Second Admission (Sept. 22 to Nov. 3, 1940).—During the ten odd years following dismissal the patient had been in general good health except for occasional colds, which tended to persist. She had no definite chronic cough, but she

recalled occasionally clearing her throat of a little blood-streaked sputum, especially in the morning. Approximately one week previous to admission she had turned over in bed, suddenly begun to cough and raised about a cupful of red blood. She had gone to her physician the next day and had been referred to the hospital in Springville for examination.

Past History: No history of erythema nodosum, erythema multiforme or definite exposure to tuberculosis could be elicited.

Physical Examination: The patient was a tall, thin woman who was not ill but had an irritating, spasmodic and slightly productive cough. The chest was symmetric, and expansion was equal on the two sides. Resonance was normal. The breath sounds at the apex of the right lung were described as rather harsh and loud as compared with those at the apex of the left lung, and voice sounds were somewhat increased over the first-named area. A few medium rales were heard over the right supraclavicular area. Examination of the blood yielded the following data: Kline reaction negative, hemoglobin content 14 Gm. per hundred



Fig. 13.—Case 13 (A. M. P.). Roentgenograms taken (A) Sept. 17, 1930 and (B) Sept. 21, 1940.

cubic centimeters, red cell count 4,130,000 and white cell count 8,800, with 66 per cent neutrophils, 27 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The appearance of the red cells was normal.

Course of Illness: The patient was placed on a regimen of modified rest in bed. Her temperature, pulse rate and respiratory rate were within normal limits. Roentgen examination of the chest revealed progressive change in the apex of the right lung since September 1930 which suggested localized dilatation of the apical bronchial tree and associated cavitation (fig. 13 B). Elsewhere the pulmonary fields were comparatively clear. On numerous occasions sputum examined by direct smear, concentration and culture was negative for tubercle bacilli. Dr. Smith reported that a specimen of sputum forwarded to him October 2 was positive for *C. immitis* and negative for *Myco. tuberculosis*.

The following cutaneous reactions were observed after admission: old tuberculin (1:100), 2 plus; occidioidin (1:1,000), 3 plus, and coccidioidin control, negative.

The results of serologic tests were reported by Dr. Smith as follows: The "complement fixation test revealed a 4 plus binding of complement through dilutions of serum down to 1:40. It was not possible to demonstrate precipitins because of contamination of the serum."

On October 28 iodized poppyseed oil was introduced into the upper part of the right bronchial tree through a small catheter, inserted in the bronchus with the patient anesthetized with pontocaine hydrochloride and maintained in a modified Trendelenburg position. The oil was seen to outline the bronchial tree extending into the upper lobe of the right lung. It flowed into the apex with some difficulty and only partly entered sacculated dilated bronchial defects in the extreme apical region corresponding to the area under observation. The clinical impression was bronchial sacculatation and dilatation (bronchiectasis, with cavitation of the apex of the right lung).

Roentgenograms taken after the patient was discharged showed evidence of some residual oil within the alveoli in the right infraclavicular area and no change in the appearance of the pathologic condition in the apex of the right lung; otherwise both pulmonary fields were clear.

When last seen, on June 20, 1941, the patient stated that she had remained well after returning home and complained only of occasional cough and sputum, which had been blood streaked on a single occasion. Her appetite and strength were good, and she had increased in weight to 150 pounds (68 Kg.). Roentgen examination revealed little change in the appearance of the pathologic condition in the apex of the right lung. A small amount of residual poppyseed oil was visible in the outer infraclavicular area. Elsewhere the pulmonary fields were clear.

Indolent apical bronchiectasis existed in the right lung for eleven years. Recovery of viable *C. immitis* from the sputum and the fixation of complement in fairly high titer identify the causative agent. Over this long period there has been no serious dissemination of the disease from its original focus. As in the cases of cavitation, the condition can best be classified as a latent primary coccidioidal infection, manifested in this case by apical bronchiectasis.

COMMENT AND SUMMARY

The thirteen cases reported here illustrate the striking ability of the body to arrest coccidioidal infection despite destructive lesions and evidence of a long existent pathologic condition. This power of arrestment, both in human beings and in animals, has been described by Cox and Smith.¹⁰ They reported 4 necropsies, during which they found fibrocaseous and calcified foci in lungs and hilar lymph nodes which contained spherules of *C. immitis*. They also observed that in one third of a group of rats inoculated with small measured numbers of spherules the resultant lesions were calcified five months or more after inoculation. In certain of the animals spherules were found deeply embedded in fibrous foci two years after inoculation.

10. Cox, A. J., and Smith, C. E.: Arrested Pulmonary Coccidioidal Granuloma, *Arch. Path.* **27**:717 (April) 1939.

Pulmonary coccidioidal cavities, such as occurred in 12 cases reported here, are characterized by quiescent roentgenographic appearance and innocuous behavior. They form easily visible localizations of primary coccidioidal infection in the lung. The concept of cavity development has been well reviewed by Eloesser.¹¹ Besides stating his own observations and conclusions, he cited the experimental work of Moolten and the theory of Reinders. According to these authors, cavitation arises from an initial small necrotic focus which produces an interruption of the unyielding pulmonary framework of the lung parenchyma. Then, because of the interplay of several factors, including elastic retraction of the surrounding resilient lung, partial bronchial obstruction and marginal atelectasis of the surrounding alveolar tissue, there results a ballooning out of the small caseonecrotic focus, which gradually assumes the proportions of a cavity. In coccidioidal infection, lack of considerable tissue destruction and peripheral inflammatory reaction produces a thin-walled structure which has somewhat the appearance of a solitary cyst. Bronchial communications may be small or large, single or multiple, and they determine whether such a cavity may be filled through the bronchial tree by radiopaque substances, such as iodized poppyseed oil. These communications also determine whether the cavity will resist closure after collapse therapy. Such cavities are to be considered as more or less benign, stabilized structures which are the end results of a small focus of destruction produced by the primary coccidioidal infection. It is conceivable that they may disappear spontaneously if bronchial occlusion becomes total and permanent. Primary infection may also become a deep-seated localized infection of the bronchial wall, eventually producing a small area of bronchiectatic change associated with destruction and sacculation of the bronchial wall, as illustrated by case 13.

With ever increasing recognition of cases of coccidioidal infection outside of California, it is important to focus attention on the pulmonary aspects of the disease, especially cavitation. Primary coccidioidomycosis occurs much more frequently than does coccidioidal granuloma, and the pulmonary cavitation, likewise, is almost exclusively associated with the primary infection, rather than with the granuloma stage. Confusion with pulmonary tuberculosis, which is closely simulated in roentgenographic appearance, must be avoided. Pulmonary cavitation associated with primary coccidioidomycosis is relatively benign as compared with the lethal cavitation occurring in tuberculosis. Prognosis is therefore decidedly favorable, and treatment should be conservative. Apparently it is not at all essential to apply the rigid code of treatment

11. Eloesser, L.: Blocked Cavities in Pulmonary Tuberculosis, *J. Thoracic Surg.* 7:2 (Oct.) 1937.

used in tuberculosis and to close the cavity by whatever means becomes necessary. From the standpoint of public health, it is not necessary to isolate the patient or to separate him long from his usual mode of living and employment. Persistent pulmonary hemorrhage or the occasional large cavity associated with spherule-laden sputum may be an indication for pneumothorax.

Careful study and observation of the 13 cases reported here form the basis for these deductions. The first case is an instance of failure to differentiate early between coccidioidal cavitation and tuberculous cavitation and thereby to protect the patient from prolonged institutional care, excessive treatment and the temporary stigma of a diagnosis of tuberculosis. Marking the pitfalls to be avoided is one of the prime purposes of this paper. In addition, attention is directed to the occurrence of a characteristic "latent" type of pulmonary cavitation in association with, or residual to, primary coccidioidomycosis. Criteria for diagnosis are outlined and the frequent occurrence of hemoptysis described. One case of apical coccidioidal bronchiectasis is also included.

Dr. C. E. Smith, Miss R. J. Wheatlake and the staff of the Department of Public Health, Stanford University School of Medicine, performed the bacteriologic studies. I was also assisted by Dr. Clara Hughes and Miss Frieda Ward, of the Tulare-Kings Counties Joint Tuberculosis Hospital.

PROGNOSTIC VALUE OF VARIOUS CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF ACUTE MYOCARDIAL INFARCTION

II. ULTIMATE PROGNOSIS

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AND

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In recent years there has been a growing appreciation of the fact that not only do patients recover from acute myocardial infarction but often they can return to a reasonably normal way of life for some years. In his report in 1912, Herrick¹ pointed out that myocardial infarction was not necessarily fatal. However, for the next fifteen years, emphasis was placed on the clinical and the electrocardiographic diagnosis of this disease, and not until recently was attention directed to the course of those patients who survived an acute episode. Interest was no doubt stimulated by isolated reports² of persons who lived long and active lives after recovering from an acute attack. In this connection, it is interesting to note that Ryle³ inferred, from Sir Everard Home's accounts, that John Hunter lived for twenty years after a typical acute coronary occlusion. However, as Levine⁴ and Levy⁵ pointed out, the prognosis in cases of coronary arterial disease remains extremely difficult. It seemed worth while to us to analyze the various clinical and electrocardiographic features of a large number of patients who had

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* **59**:2015 (Dec. 7) 1912.

2. Thayer, W. S.: Reflections on Angina Pectoris with Special Regard to Prognosis and Treatment, *Internat. Clin.* **1**:1, 1923. White, P. D.: Longevity After Coronary Thrombosis, *J. A. M. A.* **100**:233 (Jan. 28) 1933. Lewis, W. H.: Coronary Occlusion: A Report of Unusual Activities After Recovery, *ibid.* **114**: 484 (Feb. 10) 1940.

3. Ryle, J. A.: A Note on John Hunter's Cardiac Infarct, *Lancet* **1**:332 (Feb. 18) 1928.

4. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Baltimore, Williams & Wilkins Company, 1929.

5. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936, chap. 8.

recovered from what was, so far as could be determined, their first myocardial infarction, in order to discover, if possible, any clues which might lead to a more accurate prediction of the future course of the disease.

METHOD AND MATERIAL

A study was made of 372 patients, all of whom had been seen and followed in consultation practice by one of us (S. A. L.). It was felt that these patients represented a broad cross section of those who had recovered from their initial myocardial infarction, for some had had an attack requiring hospitalization, others had been treated at home and still others had been ambulatory throughout the acute episode. The exact number of subsequent attacks of coronary thrombosis was not ascertained. Of the entire group, 101 patients were followed to the time of death (average, forty-one and one-tenth months). The follow-up period for the remainder averaged twenty-seven and six-tenths months; 60 per cent of them were followed for thirteen months or more.

According to the electrocardiographic findings at the time of the acute attack or the first examination thereafter, the patients were classified into six groups based on the presence of (1) anterior infarction (145), (2) posterior infarction (110), (3) bundle branch block (14), (4) partial and (or) complete heart block (11), (5) low voltage of the QRS complex in the standard leads, with no other significant abnormality (22) and (6) defective intraventricular conduction (15). A seventh, unclassified group included those patients whose electrocardiograms showed only minor or bizarre changes (54). In addition there was 1 patient in whom occurred the electrocardiographic changes which have been described by Wood, Wolferth and Bellet⁶ as indicative of an infarction of the lateral wall of the left ventricle. For one half of all the patients electrocardiograms taken either during the acute episode or during the first month after the onset of symptoms were available for review. For the others, it was necessary that the demonstrable changes be unequivocal in order for a patient to be included in one of the first six groups just listed. The unclassified group consisted particularly of patients seen some weeks or months after the acute attack, and for most of them (78 per cent) serial electrocardiograms were not available.

DURATION OF SURVIVAL

The duration of life following the initial attack of acute coronary thrombosis has been variously reported. Bedford⁷ found the average to be six months in 31 cases but indicated that some persons might live more than five years. Wilson⁸ suggested that most patients die within two years. White⁹ reported an average survival period of three years

6. Wood, F. C.; Wolferth, C. C., and Bellet, S.: Infarction of the Lateral Wall of the Left Ventricle: Electrocardiographic Characteristics, *Am. Heart J.* **16**:387 (Oct.) 1938.

7. Bedford, D. E.: Prognosis in Coronary Thrombosis, *Lancet* **1**:223 (Jan. 26) 1935.

8. Wilson, T. E., in discussion on Clark, L. J.: Prognosis in Coronary Disease, *New Orleans M. & S. J.* **86**:365 (Dec.) 1933.

9. White, P. D.: The Prognosis in Angina Pectoris and Coronary Thrombosis, *J. A. M. A.* **87**:1525 (Nov. 6) 1926.

in 18 cases of coronary thrombosis which he selected from 160 cases of angina pectoris described by Mackenzie. For 80 patients followed by White and Bland¹⁰ the average was one and nine-tenths years, but there were 94 additional patients in their series who were still living after an average of three and two-tenths years. For the 101 patients in this study who were followed to the time of death, the average length of life after the initial attack of myocardial infarction was forty-one and one-tenth months (table 1). It was almost the same for 44 patients who had anterior infarctions (forty-two and six-tenths months) as for 27 patients who had posterior lesions (forty and nine-tenths months). Eleven patients who showed only a low voltage of the QRS complex in the standard leads lived an average of thirty-eight and three-tenths months, whereas 12 patients with electrocardiograms which we termed "unclassified" had the longest average survival, fifty-one months. For

TABLE 1.—*Duration of Survival After Acute Myocardial Infarction*

Electrocardiographic Group	Number of Patients	Average Survival Period, Months
Anterior infarction	44	42.6
Posterior infarction	27	40.9
Bundle branch block.....	2	4.0
Partial and complete heart block.....	3	15.3
Defective intraventricular conduction.....	2	44.5
Low voltage QRS in standard leads.....	11	38.3
Unclassified	12	51.0
Total.....	101	41.1

2 patients with bundle branch block, 3 with partial and (or) complete heart block and 2 with defective intraventricular conduction the average period of survival was four, fifteen and three-tenths and forty-four and five-tenths months, respectively.

Of the entire group of 101 patients known to have died, 27 per cent succumbed within one year, 47 per cent within two years and 73 per cent within five years. Four patients died ten years or more after the initial attack. The longest period of survival was twelve years, that of a man aged 36 who suffered a severe attack requiring hospitalization and yet on recovery was able to return to full activity as a traveling salesman for many years.

There were 271 patients who were still living at the time of the last follow-up information. The average period of survival for this group

10. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, *Am. Heart J.* 7:1 (Oct.) 1931.

was twenty-seven and six-tenths months. One hundred and seven patients (40 per cent) had been followed for one year or less, 58 (21 per cent) for thirteen to twenty-four months, 70 (26 per cent) for twenty-five to sixty months and 32 (12 per cent) for five to ten years. There were 4 patients (1 per cent) who were followed more than ten years. This last group included 1 man who had a definite myocardial infarction at the age of 57 but was still working and active twenty-five years later, with an occasional pill of glyceryl trinitrate for anginal pain.

At first glance it might appear that if the living patients were followed until the final outcome, the average survival period would be lengthened. From previous experience with similar problems this has not appeared to be the case when the end result for a significant number of patients is known. It must be borne in mind that among those that are still living there are a good many who have so far survived only a few months and are likely to die within a year or two, thus counterbalancing some that have survived for more than ten years. We, therefore, are of the opinion that the average figure of forty-one and one-tenth months, as given previously, is valid. This is in accord with results of an earlier study,¹¹ in which the survival after the first attack of coronary thrombosis of patients with angina pectoris was found to be between three and three and five-tenths years.

SUBSEQUENT ANGINA PECTORIS

Results of previous studies regarding the occurrence of angina pectoris following recovery from acute coronary thrombosis show a rather wide variation, possibly due to the fact that no differentiation was made between those patients suffering initial attacks and those with recurrent episodes. Willius¹² found that 45 per cent of his patients experienced subsequent angina. Hochrein and Schneyer¹³ reported it in 26 per cent of their patients who recovered. Padilla and Cossio¹⁴ stated that six months after the attack 5 per cent of their patients suffered from angina pectoris.

In this series angina pectoris was present some time after the attack in 63 per cent of all the patients. The interval between the attack

11. Eppinger, E. C., and Levine, S. A.: Angina Pectoris: Some Clinical Considerations with Special Reference to Prognosis, *Arch. Int. Med.* **53**:120 (Jan.) 1934.

12. Willius, F. A.: Life Expectancy in Coronary Thrombosis, *J. A. M. A.* **106**:1890 (May 30) 1936.

13. Hochrein, M., and Schneyer, K.: Das Schicksal des Myocardinfarktes, *Ztschr. f. Kreislaufforsch.* **28**:257 (April 15) 1936.

14. Padilla, T., and Cossio, P.: Pronostico del infarto de miocardio, *Rev. argent. de cardiol.* **1**:181 (July-Aug.) 1934.

and the appearance of angina was variable. In some persons it persisted throughout the acute episode and into convalescence, without remissions. In others the cardiac pain did not make its appearance for several years after the initial episode. This symptom was found to develop with equal frequency in each of the various electrocardiographic groups, except that it was somewhat more common in the unclassified group and less common in the one characterized by a low voltage of the QRS complex in the standard leads. Furthermore, the average severity of the angina, when it did make its appearance, was approximately the same throughout the various electrocardiographic groups, if it was classified on a scale of absent, mild, moderate, marked and severe, depending on the degree of activity required to bring on distress. In addition, it was seen that for 25 patients who died without experiencing subsequent angina pectoris, the average duration of survival was the same (forty-three months) as it was for 67 patients known to have

TABLE 2.—*Relation of Age at Time of Initial Attack to Duration of Survival*

Age, Year	Number of Patients	Average Survival Period, Months
30-39	5	63.0
40-49	24	54.8
50-59	36	37.6
60-69	30	29.9
70-79	4*	43.5

* One patient in this age group survived one hundred and thirty-eight months.

manifested this symptom at some time before death (forty-three and one-tenth months). It would appear, therefore, that on the whole the electrographic pattern at the time of the initial myocardial infarction does not permit, of itself, a prediction regarding the presence or absence of subsequent angina pectoris, nor does the development of this symptom at some time after the recovery make possible any estimate regarding the length of life which may be expected.

SUBSEQUENT CONGESTIVE HEART FAILURE

Padilla and Cossio¹⁴ found that 9 per cent of their patients had congestive failure six months after the acute attack. Of the 169 patients whom Willius¹² followed, 3.6 per cent became bedridden because of congestive failure. In our series there were 364 patients for whom there was definite information regarding subsequent decompensation. Their conditions were classified as one of five degrees: absent, mild, moderate, marked and severe. In 72 per cent of the total series heart failure was absent, in 19 per cent it was mild or moderate and in 9 per cent it was marked or severe. When only those patients who were known to have died were considered, there were 57 per cent who showed

no evidence of decompensation up to the time of the final illness, 18 per cent who had mild or moderate congestive failure and 25 per cent in whom the failure was marked or severe.

A similar analysis of each electrocardiographic group indicated that the average degree of subsequent congestive failure was somewhat greater in those patients whose original lesion was anterior than in those in whom it was posterior. This is in accord with the impression expressed by Wood and his associates¹⁵ that recovery of cardiac function was more rapid and complete after posterior than after anterior infarction. Some evidence of congestive failure appeared in 35 per cent of patients with an anterior lesion and in 14 per cent of those with a posterior infarct. In the groups who showed bundle branch block, defective intraventricular conduction or low voltage the incidence was 49 per cent.

A further check of the patients who were known to have died revealed that those who showed no evidence of congestive failure up to the time of the terminal event had an average survival period of forty-five and seven-tenths months, as compared with that of thirty-six and eight-tenths months for those who had shown some signs of decompensation.

It may be concluded, therefore, that after the initial attack of myocardial infarction some evidence of congestive failure develops in slightly less than one-half the patients before they die and that those in whom heart failure appears tend to have a shorter life span. Furthermore, decompensation occurs somewhat more frequently after anterior than after posterior infarction.

RECOVERY OF ACTIVITY

Previous investigations regarding ability to resume activity after recovery from an acute coronary thrombosis have each yielded practically the same results. Conner and Holt¹⁶ reported that 86 per cent of their patients were essentially well after six months, 42 per cent after three years and 21 per cent after five years. Of the patients followed by Cooksey,¹⁷ 78.1 per cent were restored to their previous occupation. Willius¹² found that 75.7 per cent were restored to good health or were well with restrictions. More recently Master and Dack¹⁸ have pointed

15. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observation on the Use of Chest Leads, *Arch. Int. Med.* **52**:752 (Nov.) 1933.

16. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, *Am. Heart J.* **5**:705 (Aug.) 1930.

17. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Especial Reference to Prognosis, *J. A. M. A.* **104**:2063 (June 8) 1935.

18. Master, A. M., and Dack, S.: Rehabilitation Following Acute Coronary Artery Occlusion, *J. A. M. A.* **115**:828 (Sept. 7) 1940.

out that 59 per cent of their patients were able to return to work after the first attack.

In this series information regarding the subsequent degree of activity was available for 354 patients. The capacity of each was classified as one of four degrees: essentially full activity, slightly restricted activity, moderately restricted activity and complete incapacitation. It was found that 30 per cent of all patients were able to return to work and to full duty at least for an appreciable length of time, 45 per cent to partial activity and 22 per cent to moderately restricted activity. Only 3 per cent were completely incapacitated. In this analysis we have considered the state of activity maintained for some months after the first attack. This obviously would be altered by secondary attacks or progressive myocardial impairment as time went on. Although the effect of subsequent attacks was not studied in detail, it did appear, as Master and Dack have indicated, that the degree of recovery grew progressively less with each bout of acute myocardial infarction.

The degree of recovery in patients with anterior infarction was slightly less than in those with a posterior lesion, 72 per cent of the former returning to full or partial duty, as compared with 86 per cent of the latter. Patients who had electrocardiograms showing partial and (or) complete heart block or only low voltage of the QRS complex suffered a greater than average degree of subsequent restriction.

It appears, then, that three fourths of the patients who recover from their first attack of acute coronary thrombosis are able to resume full or partial activity and that a greater number of those with posterior infarction are able to do so than of those whose electrocardiograms indicate another type of lesion.

SEX

As in most large series of cases of acute myocardial infarction, there was a striking predominance of men (89 per cent of 372 patients). In an earlier but less extensive study⁴ it was also suspected that women were not apt to remain in as good health for as long a time as men. However, White and Bland¹⁰ and Padilla and Cossio¹⁴ reported that sex was unimportant in the prognosis of coronary thrombosis. This has not been true in the present analysis. For 89 men followed to the time of death the average survival was forty-four and two-tenths months, whereas, for 12 women known to have died the average survival after the initial myocardial infarction was eighteen and three-tenths months. It might be said that this discrepancy is accounted for by the fact that the male patients include all those who were between the ages of 30 and 40 at the time of their first attack and that, as will be pointed out, patients of such age have a longer subsequent expectancy. However, after excluding all who fell into this age group at the onset, we found

that the average survival period for men was forty-three and one-tenth months, a value still definitely above that for women. Of the women known to have died, none lived more than five years. Two of the 30 women still living at the time of the last follow-up observation indicate that occasionally a long survival can occur; 1 woman was still fairly active after nearly fifteen years, and the other had lived nine years.

In the determinations of the frequency and degree of angina pectoris experienced subsequent to recovery in the two sexes, it seemed that the averages for men and for women were nearly the same. In general, this held true irrespective of the electrocardiographic pattern, with the possible exception that the small groups of women who had an anterior

TABLE 3.—*Comparison of Blood Pressures Before and After Acute Myocardial Infarction*

Before Attack		Few Months After Attack		Last Blood Pressure Recorded (One to Several Years After Attack)	
Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
170	110 ($\frac{1}{2}$)*	170	100 (13)*	180	90 (32)*
185	90 (13)	140	80 (7)	170	80 (32)
240	120 ($\frac{1}{4}$)	140	80 (8)	180	70 (19)
210†	145 ($\frac{1}{4}$)	200	150 (4)	210	140 (12)
160	90 (2)	140	85 (11)	180	120 (14)
180†	90 (6)	140	90 (2)	190	95 (25)
160†	100 ($\frac{1}{4}$)	130	80 (2)	155	80 (13)
140	80 (10)	120	60 (2)	155	85 (38)
180†	110 ($\frac{1}{4}$)	155	100 (2)	155	110 (10)
192†	125 ($\frac{1}{2}$)	142	94 (2)	150	98 (24)
162†	95 (5)	130	80 (4)	130	78 (12)
160	100 (24)	140	100 (19)	150	90 (31)
200	100 (22)	190	90 (4)	200	100 (6)
156	82 (11)	148	110 (2)	148	92 (6)
210	160 (5)	210	140 (4)	185	140 (7)
210†	115 ($\frac{1}{4}$)	210	130 (1)	232	136 (36)
Average	182	156	96	173	100

* Numbers in parentheses indicate time in months before or after attack.

† In this case blood pressure readings were known within a few weeks or months before the attack and during the subsequent months and years.

lesion, partial and (or) complete block or defective intraventricular conduction had somewhat more severe angina than men who showed the same type of tracing with their acute attacks.

On the other hand, it was found that the average degree of congestive failure which appeared after recovery from an initial myocardial infarction was definitely greater in women than in men. Of the former 72 per cent had no or only mild decompensation while for men the corresponding figure was 86 per cent. This feature was especially noticeable if the infarction originally present was located posteriorly or if the electrocardiograms had shown bundle branch block, auriculoventricular block or a low voltage of the QRS complex in the standard leads. The greater frequency of heart failure among women may well be accounted for by the greater prevalence of hypertension.

Master and Dack¹⁸ have reported that sex was not a factor in influencing return to work. However, the average degree of recovery of activity was definitely greater in men than in women in this series. This was further brought out by the evidence that 79 per cent of the men were able to return to full or partial activity whereas only 51 per cent of the women had that degree of recovery of function. Here, again, this variation held true no matter what the electrocardiographic pattern may have been, with the exception of those patients with tracings of the unclassified type. In that group the average degree of recovery was equal for the two sexes.

It may be said, therefore, that after recovery from an initial myocardial infarction women, as compared with men, tend to live a shorter time, have more congestive failure and are less able to return to a useful degree of activity.

AGE

In regard to age statistics, study of this series of patients yielded much the same results as would a study of any large group of persons with initial acute coronary thrombosis. The average age at the time of the attack for all patients was 53.9 years. The average age of the men was 53.3 years and of the women 58.9 years. Of the women, 86 per cent were 50 years of age or over, as contrasted with 65 per cent of the men. Twenty patients (5 per cent), all men, were in the decade from 30 to 39.

The frequency and severity of subsequent angina pectoris were determined for patients in each decade. It was found that the average severity of subsequent cardiac pain was less in the 30 to 39 year age group than in the 40 to 49 and 50 to 59 year age groups, but was approximately the same as that experienced by patients over the age of 60. In addition, 80 per cent of the patients who made up the 30 to 39 year age group had no or mild subsequent angina pectoris, as compared with 69 per cent of all other patients.

The frequency and the severity of subsequent congestive failure were determined for patients in each decade. It appeared that, in general, the average degree of subsequent heart failure rose progressively with the age at the onset of the attack. Of those patients in the decade 30 to 39, 85 per cent had no subsequent heart failure, whereas corresponding results for the other age groups were 75 per cent for the decade 40 to 59 and 62 per cent for the decade 60 to 79.

Cooksey¹⁷ reported that younger persons were more regularly able to resume a fuller share of previous activity after recovery than were older patients. Master and Dack¹⁸ also found this to be the case and expressed the belief that the age of the patient was the most important factor in determining return to work. Our analysis has yielded a

that the average survival period for men was forty-three and one-tenth months, a value still definitely above that for women. Of the women known to have died, none lived more than five years. Two of the 30 women still living at the time of the last follow-up observation indicate that occasionally a long survival can occur; 1 woman was still fairly active after nearly fifteen years, and the other had lived nine years.

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In regard to age statistics, study of this series of patients yielded much the same results as would a study of any large group of persons with initial acute coronary thrombosis. The average age at the time of the attack for all patients was 53.9 years. The average age of the men was 53.3 years and of the women 58.9 years. Of the women, 86 per cent were 50 years of age or over, as contrasted with 65 per cent of the men. Twenty patients (5 per cent), all men, were in the decade from 30 to 39.

The frequency and severity of subsequent angina pectoris were determined for patients in each decade. It was found that the average severity of subsequent cardiac pain was less in the 30 to 39 year age group than in the 40 to 49 and 50 to 59 year age groups, but was approximately the same as that experienced by patients over the age of 60. In addition, 80 per cent of the patients who made up the 30 to 39 year age group had no or mild subsequent angina pectoris, as compared with 69 per cent of all other patients.

The frequency and the severity of subsequent congestive failure were determined for patients in each decade. It appeared that, in general, the average degree of subsequent heart failure rose progressively with the age at the onset of the attack. Of those patients in the decade 30 to 39, 85 per cent had no subsequent heart failure, whereas corresponding results for the other age groups were 75 per cent for the decade 40 to 59 and 62 per cent for the decade 60 to 79.

Cooksey¹⁷ reported that younger persons were more regularly able to resume a fuller share of previous activity after recovery than were older patients. Master and Dack¹⁸ also found this to be the case and expressed the belief that the age of the patient was the most important factor in determining return to work. Our analysis has yielded a

similar result. The average degree of recovery of activity grew progressively smaller with advancing age, and the number of those able to return to work became less and less with each decade. Of the patients who were between 30 and 39 years old, 65 per cent returned to full duty, as contrasted with 39 per cent of those between 40 and 49, 26 per cent of those between 50 and 59 and 29 per cent of those who were 60 or older.

White and Bland¹⁰ expressed the opinion that young patients lived longer, as a rule, after suffering an acute coronary thrombosis. This belief was later supported by observations of Glendy, Levine and White.¹⁹ In their study of patients with angina pectoris, Eppinger and Levine¹¹ found that those whose symptoms began before the age of 50 lived two and three-tenths years longer than those whose pain first appeared after that age. On the other hand, Padilla and Cossio¹⁴ concluded that age made no difference in the prognosis. In this study we have analyzed the group of patients who were known to have died to determine the influence of the age at the time of the attack on the subsequent duration of survival. It was evident that the younger patients lived longer than the older ones (table 2). Five patients who were between 30 and 39 years of age lived an average of sixty-three months. For 24 patients who were in the 40 to 49 year decade the average subsequent life span was fifty-four and eight-tenths months. For 36 patients between 50 and 59 years old it was thirty-seven and six-tenths months, while for 30 patients in the 60 to 69 year age group it was twenty-nine and nine-tenths months. There were 4 patients in the 70 to 79 year decade with an average survival of forty-three and five-tenths months; this figure would have been much lower but for a 72 year old man who lived one hundred and thirty-eight months after his attack.

In summary, it is clear that after recovery from acute coronary thrombosis younger patients have less subsequent angina or congestive heart failure and as a rule live longer and more useful lives than do older patients.

SEVERITY OF ORIGINAL ATTACK

It seemed worth while to determine whether the severity of the manifestations during the initial acute myocardial infarction offered any indication regarding the course that followed recovery. For each patient the gravity of the acute episode was classified as mild, moderate, severe or extremely severe. In this classification, various features, such as severity and duration of pain, amount of dyspnea, degree of shock and

19. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth: Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, *J. A. M. A.* **109**:1175 (Nov. 27) 1937.

evidence of pulmonary congestion, were evaluated. It was seen that the average severity of the initial attack was the same for each of the electrocardiographic groups. On the whole, this was true as well for each age group.

The severity of the original episode bore little relation to the subsequent angina pectoris which patients in the various groups experienced, inasmuch as the average degree of subsequent cardiac pain was the same in those with mild attacks as in those whose attacks were considered severe. The only significant variation here was that the patients with a severe attack in conjunction with anterior infarction tended to have more intense angina pectoris afterward than those with an original episode of the same degree resulting from a posterior lesion.

The severity of the manifestations of the original acute coronary thrombosis did bear some relation to the subsequent degree of congestive failure, however, for the more severe the initial bout the greater the later decompensation tended to be. In addition, this observation held generally true in each of the electrocardiographic groups. This relation was valid as well when an analysis was made of the degree of subsequent recovery of activity in each of the four classified groups. It was seen that the patients who had mild or moderate attacks were able to resume a greater degree of activity than those who had severe or extremely severe attacks. This was true whether the infarction was located anteriorly or posteriorly. However, in those with bundle branch block or heart block the subsequent limitation of activity was great no matter how severe the original episode.

Willius¹² expressed the opinion that there was no correlation between the duration of the pain with the attack and the duration of survival. Utilizing the survival periods for those patients who were known to have died, we observed that for 11 patients with mild attacks the average survival was thirty-five and eight-tenths months, for 69 patients with moderate attacks forty-three and eight-tenths months and for 18 patients with severe attacks thirty-five and two-tenths months, while 2 patients who had extremely severe attacks died after an average period of twenty-eight months. In individual cases this absence of any close correlation was even more striking, for frequently patients with mild attacks died within two or three months while others with severe attacks lived as long as twelve years.

From the foregoing data it follows that the severity of the acute attack bears no significant relation to the degree of subsequent angina or the duration of survival. There is a greater incidence of congestive failure and physical disability in those with the more severe initial episodes.

COMPLICATIONS OF ATTACK

There were 16 patients of the entire series who were known to have shown transient auricular fibrillation at the time of the acute attack. It was interesting to analyze the subsequent course of their disease. The average degree of subsequent angina pectoris experienced by these patients was definitely less than the average for all. The average degree of subsequent congestive failure for this number was higher than for those who showed no fibrillation. The average degree of recovery of activity for this group was slightly less than that for all the patients. There were 6 patients with transient auricular fibrillation who were followed to the time of death. Their average length of life was sixty-four and five-tenths months. In addition, for the 10 patients who were still living at the time of the last follow-up information, the average survival period was forty-one and two-tenths months. Although the number of patients is small, the results suggest strongly that those who have transient auricular fibrillation with the initial myocardial infarction have less subsequent angina pectoris, slightly more congestive failure and physical incapacitation and the same, or an even longer, duration of life than patients who do not show this arrhythmia.

In 29 patients of the total of 372, a pericardial friction rub was heard during the acute illness. Of this number, 17 had an anterior infarct, 7 had a posterior lesion, 1 showed bundle branch block, 2 had low voltage of the QRS complex and 2 fell into the unclassified group. So far as subsequent angina pectoris is concerned, these patients were no different from all others. There was a tendency for them to have more congestive failure, however, 66 per cent having no or mild decompensation, as compared with 86 per cent for all others. Moreover, only 64 per cent of these patients returned to full or partial activity, as compared with 76 per cent for all others. Thirteen who showed pericardial friction with the initial attack were followed to the time of death. Their average survival period was forty-one and one-tenth months, exactly the same as that for all other patients. It may be said, then, that the appearance of a pericardial friction rub during the acute phase may possibly point to a greater degree of heart failure and a lesser degree of resumption of activity after recovery, but that it does not otherwise influence the subsequent course.

Four patients were known to have had paroxysmal ventricular tachycardia at the time of the acute attack. Although they were few, their subsequent course did not differ greatly from the average, and of the 2 known to have died the survival periods were three and ninety-seven months, respectively. The last observation indicates that the development of this arrhythmia during an acute infarction is not incompatible with a reasonably long and useful survival period. In 4

patients who showed mental disturbances during the acute phases of their disease the subsequent course was no different than that in the majority of other patients. Three of them were able to return to partial work and were still living after two years. The fourth was completely incapacitated and died after three months. It was our experience that if a fairly satisfactory recovery of cardiac function resulted, any psychosis which might have been present entirely disappeared.

PREVIOUS ANGINA PECTORIS

Previous reports concerning the incidence of angina pectoris prior to acute coronary occlusion have yielded results ranging from 22.4¹² to approximately 50 per cent.²⁰ Adequate information regarding the presence or absence of previous cardiac pain was available for 288 patients in this series. Of the total, 38 per cent had definite previous angina pectoris, 10 per cent had noted atypical distress prior to the attack and 52 per cent gave no history of antecedent cardiac pain.

Conner and Holt¹⁰ found that in 22 cases there were 8 in which the pain ceased after the attack, 5 in which it was worse, 2 in which it was less and 7 in which there was no change. Willius¹² reported that although the incidence of subsequent angina in his patients was 45.1 per cent, it was only 32.4 per cent in those who had not had distress prior to the attack. The review of this series has shown somewhat similar results. The average severity of subsequent angina pectoris in those who gave a history of definite or probable previous angina was greater than in those who had noted no antecedent pain. Furthermore, of the former patients only 22 per cent had no subsequent angina, whereas of those who had no previous pain, 44 per cent also had none after recovery. As a corollary, it may be said that in 37 per cent of the entire series angina pectoris first appeared after recovery from acute myocardial infarction. It also was found that the average degree of subsequent congestive failure and limitation of activity was greater for those who gave a history of angina prior to the initial acute coronary thrombosis.

White and Bland¹⁰ have stated that the previous occurrence or duration of angina pectoris does not affect the prognosis of coronary thrombosis. In this series data regarding previous angina pectoris were available for 70 of the patients followed to the time of death. For 34 patients with typical previous distress, the average period of survival was thirty-six and two-tenths months. Six patients with atypical

20. Smith, F. M.; Rathe, H. W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, *J. A. M. A.* **105:2** (July 6) 1935. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, *Lancet* **1:4** (Jan. 7) 1928.

antecedent pain had an average survival period of fifty-seven and eight-tenths months. The average subsequent life span of 30 patients who had no angina prior to the initial episode was thirty-eight and six-tenths months.

These results indicate, therefore, that patients who have angina pectoris prior to their initial myocardial infarction have more subsequent cardiac pain and congestive failure and a lesser degree of recovery of activity. However, although they are somewhat more uncomfortable and less active, their period of survival is not particularly shorter than that of patients who have been free of pain prior to their infarction.

CHANGES IN BLOOD PRESSURE

It has been generally recognized that a fall in blood pressure is a common accompaniment of an acute myocardial infarction. This lowering of the pressure is usually found to persist during the early weeks of illness, while the patient is still in bed. It is possibly this fact which has given rise to the feeling that the blood pressure is commonly lowered permanently. In fact, it has been observed that frequently the blood pressure is decidedly lower for some months after recovery has taken place, even when the patient is ambulatory and fairly active.²¹ Little attention has been given to the ultimate changes in the blood pressure observed after following such patients for long periods.

Among those patients analyzed in part 1 of this study,²² there were 16 for whom blood pressure readings taken before the attack and those taken some months or years after recovery had taken place (table 3) were available. For 7 of them, the readings were known within a few weeks to not more than a few months before the attack and throughout a period of months to years thereafter. The average determinations for the entire group of 16 and those for the smaller but more detailed subgroup of 7 followed an almost identical pattern. The levels before the attack in the group and the subgroup, respectively, were 182 and 185 systolic and 107 and 110 diastolic. A few months after the attack the corresponding averages were 156 and 158 and 98 and 103. A year or more later they were 173 and 175 and 100 and 107. There were, however, distinct variations among the different patients, so that in some the pressure returned to approximately the original state within a few

21. Levine, S. A.: Cases of Coronary Occlusion with Recovery, *M. Clin. North America* 8:1719 (May) 1925. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: Circulatory Dynamics in Myocardial Infarction, *Arch. Int. Med.* 54:997 (Dec.) 1934.

22. Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features in Acute Myocardial Infarction: I. Immediate Prognosis, *Arch. Int. Med.* 68:913 (Nov.) 1941.

weeks whereas in others it did so only after some months, or occasionally a year or two. In fact, it is not infrequently observed that the pressure after a temporary fall may rise to the previous levels during the early days after the onset of the acute myocardial infarction. It is of some interest that in only 3 of the 16 patients was the systolic blood pressure 30 mm. or more lower a year or two after the attack than it had been before. The conclusion may be drawn from this analysis that after a temporary fall in pressure there is a tendency over the following months for a gradual return to approximately the original level.

MODE OF DEATH

Willius¹² reported that of 201 patients with coronary thrombosis, 191 died of causes related to the heart, whereas 10 died of causes unrelated to the heart. Hochrein and Schneyer¹³ have also studied this problem, with results of the same order as those in our analysis. Of the 101 patients known to have died, information regarding the nature of the terminal event was available for 80. Of this number 32 (40 per cent) died as a result of a subsequent attack of myocardial infarction, 28 (35 per cent) died suddenly and unexpectedly and 16 (20 per cent) died of congestive heart failure. There were only 4 patients (5 per cent) who died of causes unrelated to the heart, 1 of mesenteric thrombosis, 1 of a bronchogenic carcinoma, 1 of a renal neoplasm and the last as the result of a peculiar, undiagnosed febrile illness.

SUMMARY AND CONCLUSION

A study was made of 372 patients who had recovered from an initial attack of acute myocardial infarction, in order to determine the type of progress that might be expected and to see whether any predictions as to prognosis could be made from the various clinical and electrocardiographic features.

Duration of Survival.—The average period of survival of 101 patients known to have died was forty-one and one-tenth months. There was a negligible difference in the length of survival between patients with anterior and those with posterior infarction (forty-two and six-tenths and forty and nine-tenths months, respectively). The survival period for those showing QRS complexes of low voltage was thirty-eight and three-tenths months, while in the group with electrocardiograms called unclassified (showing minor alterations in the ventricular complex) it was fifty-one months.

Of 101 patients known to have died, approximately one-fourth succumbed within one year, one-half within the first two years and three-fourths within the first five years. The remainder died after

varying intervals, which ranged from five to twelve years. One of the living patients was still carrying on twenty-five years after the initial attack.

Subsequent Angina Pectoris.—Sixty-three per cent of all patients manifested angina pectoris some time after the initial attack of myocardial infarction. The onset of this symptom varied from the early days of the acute illness to years after recovery. There were only slight variations in the incidence and severity of this complaint in the various electrocardiographic groups. The presence or absence of subsequent angina did not influence the period of survival.

Subsequent Congestive Failure.—Only 28 per cent of all patients had subsequent congestive heart failure; in 19 per cent it was mild or moderate, and in 9 per cent it was marked or severe. When only those known to have died are considered, the incidence of decompensation was greater (43 per cent). The frequency of heart failure was distinctly greater with anterior infarction (35 per cent) than with a posterior lesion (14 per cent). It was greater still in the groups showing bundle branch block, defective intraventricular conduction and low voltage (49 per cent). The average survival periods with and without heart failure were thirty-six and eight-tenths and forty-five and seven-tenths months, respectively.

Recovery of Activity.—The subsequent degree of physical activity was known for 354 patients. Thirty per cent returned to essentially full duty, 45 per cent to partial activity and 22 per cent to moderately restricted activity for an appreciable length of time before a further major setback occurred. In this regard patients with an anterior lesion did less well than those with a posterior lesion. Patients with heart block or curves of low voltage were particularly limited.

Sex.—The average survival period for men was forty-four and two-tenths months and for women eighteen and three-tenths months. The occurrence of subsequent angina was essentially the same for the two sexes. Congestive failure and limitation of physical activity were distinctly greater in women.

Age.—The average age for men was 53.3 years and for women 58.9 years. The severity of subsequent angina was found to be less in those under 40 and over 60 than in those between these two ages. The degree of congestive failure and physical disability rose progressively with advancing years. The younger patients had a distinctly longer survival period than the older ones. The average progressively decreased from sixty-three months for those under 40 years of age to about thirty months for those over 60 years of age.

Severity of Original Attack.—The severity of the initial attack of acute coronary thrombosis was not a measure of the degree of sub-

sequent angina or the duration of survival. The more severe initial episodes were followed by a greater incidence of congestive failure and physical disability.

Auricular Fibrillation.—The follow-up study of 16 patients who showed transient auricular fibrillation during the acute attack indicated that they seemed to have less subsequent angina pectoris, slightly more congestive failure but about the same duration of survival as those who did not show this arrhythmia.

Pericardial Friction Rub.—The 29 patients who had pericardial friction with the initial attack displayed no more angina, tended to have slightly more congestive failure and were slightly more incapacitated than were those who did not manifest this sign, but the patients had the same survival period.

Other Complications.—The few patients who recovered after having paroxysmal ventricular tachycardia or a psychosis with the acute attack did about as well as the average for the entire series.

Previous Angina Pectoris.—The presence of angina pectoris before the attack of acute myocardial infarction rendered patients more likely to have subsequent angina, decompensation and limitation of activity but did not shorten the survival period.

Blood Pressure.—For 16 patients there were data concerning the blood pressure shortly before, several months after and one or more years after the attack of acute myocardial infarction. The averages for the three readings were 182, 156 and 173 systolic and 107, 98 and 100 diastolic, respectively. There were individual variations, so that in some the pressure returned to approximately the original level very quickly and in others only after a year or two.

Mode of Death.—Of the 80 patients for whom the mode of death was known, 40 per cent died of a subsequent attack of myocardial infarction, 35 per cent died suddenly, 20 per cent died of congestive failure and only 5 per cent died of a cause unrelated to the heart.

Conclusion.—It may be stated that, although the course that follows an acute myocardial infarction varies a great deal, there are some clinical features analyzed in this study which may aid materially in judging the prognosis.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1941

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WAR NEUROSES

Before 1915 neurosis was a disorder respected and studied by some specialists in neuropsychiatry but belittled by most physicians as something "imaginary" or "weak." Their attitude toward this ill often smacked of the moralistic; the patient "ought to snap out of it" if he "only had the guts." The patients, too, sometimes felt that their troubles were not medical, but moral or spiritual, and kept away from psychiatrists because they did not want to admit to themselves and others that there was anything wrong with their "minds."

All this was greatly changed by the war experience. Severe neurotic symptoms soon began to appear among officers and men. At first they were explained as "shell shock," the implication being that there was concussion of the central nervous system. This explanation was found to be wrong except in a small number of cases. Three to 9 per cent of all casualties were recognized as psychogenic. In the American Expeditionary Force the total was about 33,000. In England in 1921, pensions were being given to 65,000 veterans for psychogenic disorders (exclusive of some 32,000 with cardiac neuroses).

All this has greatly altered the attitude of members of the medical profession toward neurosis. In the first place, these symptoms often appeared in men who were considered brave and strong; excellent officers were often affected. The moralistic attitude was manifestly nonsensical. As time went on the psychologic mechanisms concerned in some cases became obvious to a large number of medical officers. They had the personal experience of seeing how emotional stress would precipitate stupor, tremors, blindness, deafness, paralyses, fits, fugues and cardiac, respiratory, gastrointestinal and genitourinary symptoms. This experience caused a remarkable advance in psychiatry during the years following the war. Now another war is on, and the same problem is cropping up in new and old forms.

Realization of the importance of organizing the knowledge of the past experiences and learning quickly from the new has resulted in

the appearance of several important reviews and papers. Miller¹ has edited a book on "The Neuroses in War," made up of well coordinated chapters by a number of experienced Englishmen. Zabriskie and Brush² have done a fine piece of work in a 35 page review of "Psychoneuroses in War Time." Kardiner³ has written a long monograph on "The Traumatic Neuroses of War." Besides these three long contributions, there are a number of shorter recent papers telling of the current experiences of this war,⁴ which differ from experiences of earlier wars principally in the fact that civil populations are now also exposed to the horrors of bombing, machine gun fire and incendiarism.

To one who has looked through hundreds of pages of this interesting, but somewhat discursive and repetitive, material, the impossibility of an accurate review is obvious. One can, however, put down what seems to be the consensus and the more advanced ideas.

Etiology.—Heredity plays a part only in that some men are born with more sensitive nervous systems than others. If the strain imposed on an average, sound soldier is severe enough, he can break. The earlier existence of neurotic symptoms in civil life predisposes to their reappearance under stress of war, and a lesser stress than would be needed to break a sounder man may well throw a predisposed soldier into neurotic reactions. Of course, because of past experiences and individual conditioning, strain to one man is not strain to another, at least not to the same degree. The main common denominator is the internal conflict of the soldier between the instinct of self preservation and the social urge to carry on: fear versus duty. Other common conflicts are with discipline, dirt and killing. In some persons with much "repressed aggression" killing may lead to great anxiety and complete invalidism. It seems that their whole carefully built up education against cruelty breaks down and gives them insight into what cruelties they might perform if let loose. This they recognize as entirely incompatible with the personal integration they have achieved, and the conflict becomes unbearable.

1. Miller, E.: *The Neuroses in War*, New York, The Macmillan Company, 1940.

2. Zabriskie, E. G., and Brush, A. L.: *Psychoneuroses in War Time*, *Psychosom. Med.* **3**:295-329, 1941.

3. Kardiner, A.: *The Traumatic Neuroses of War*, *Psychosomatic Medicine Monograph II-III*, New York, Paul B. Hoeber, Inc., 1941.

4. (a) Culpin, M.: *A Week-End with the War Neuroses*, *Lancet* **2**:257, 1940. (b) Debenham, G.; Sargant, W.; Hill, D., and Slater, E.: *Treatment of War Neurosis*, *ibid.* **1**:107, 1941. (c) Slater, E., and Sargant, W.: *Acute War Neuroses*, *ibid.* **2**:1, 1940. (d) Wittkower, E., and Spillane, J. P.: *Neuroses in War: Part I*, *Brit. M. J.* **1**:223, 1940. (e) Wittkower, E., and Spillane, J. P.: *Neuroses in War: Part II*, *ibid.* **1**:265, 1940.

Fatigue, poor diet, sleeplessness and illness may all lead to a state of exhaustion that predisposes to psychogenic troubles. The main sources of strain are danger of death, guilt over killing, responsibility, separation from family and sexual deprivation. It has been found that the type of man most likely to break down is the unsociable fellow who is self centered and overconscientious.

Clinical Picture.—This is too complex and varied to describe in brief. Almost any symptom may appear. The commonest categories are the rather simple conversion hysterias (found mostly among enlisted men) and the difficult anxiety states (found more often among officers). Here should be mentioned the "effort syndrome" (soldiers' heart, "D. A. H."); it seems probable that these three terms are synonyms for "anxiety neurosis"; so the total psychoneurotic casualties of the British and American armies in the last war ought probably to be increased by some 20,000 or 30,000 officially classed as "cardiovascular." In the light of present knowledge these are almost certainly disorders of the autonomic nervous system, expressed by fatigability, breathlessness, palpitation, precordial pain, dizziness, blurred vision, sweating and vasomotor disturbances.

The prodromal signs are important. Men likely to break down can often be recognized beforehand by complaints of fatigue, increased use of alcohol and tobacco, irritability, unsociability, dulness, crying spells and sweating.

The new thing in this war seems to be the greater number of cases in which mental confusion and stupor form the center of the clinical picture. Some men, especially those seen after the evacuation of Dunkerque,^{4c} showed extreme exhaustion and tension; they had tremor and such tense muscles in limbs and face that they were sometimes thought to have paralysis agitans. A great number of psychosomatic syndromes are also being recognized. This is probably not a new situation but a new point of view that admits the possibility of psychologic causes behind gastrointestinal, genitourinary, cutaneous, intestinal and cardiac symptoms. Gastric ulcer is a great problem at present.

Prevention.—It is, of course, important to prevent the nervously unfit from entering the armed forces, probably even more so in the navy than in the army. This can be done only by proper examination of recruits by men who know how to elicit and evaluate a history of neurosis. It is also important to have the draft board examiners realize that the government is now paying pensions to thousands of psychoneurotic veterans who should never have been let into the army. The attitude is too common that a man who is willing to tell of nervous symptoms is malingering and that the army "will do him good." The

fact is that he will do the army no good, and even if he is malingering, the army certainly does not want him.

In the routine of army life it is important to have proper periods for rest and recreation. Of course war is the most stressful phenomenon known and this cannot be modified, but whenever possible periods of tension should be shortened. Also, recreation should be such as to give the men satisfaction; amusements are not enough and often lead to disgust and depression. All this is in the sphere of the morale officer. The medical officer, however, may perform an important prophylactic function by talking to officers and men on the physiology of fear. One might as well admit frankly that every one is afraid of death and that the symptoms are universal. It is better to have the men recognize this than to add to their natural fear reaction the worry over symptoms. Many a man has thought he might be going to drop dead of heart disease because he had palpitation, and many others have mistaken emotional diarrhea for "cholera morbus."

Treatment.—There is great unanimity among the various authors in urging early and adequate treatment. If the patient can be seen by a psychiatrist within thirty-six hours of the onset of severe symptoms, the likelihood of quick recovery is greatly increased. Full diet and forcing of fluids are usually important, for exhaustion and dehydration have often been mistaken for severe neurosis. Narcosis is used freely. This is probably necessary in smaller hospitals, but in base hospitals hydrotherapy should be available. Sometimes the aforementioned regimen, with long hours of sleep, induced by barbiturates if necessary, will largely clear up the symptoms.

In most cases, however, psychotherapy is also needed. If the patient is in good rapport he can immediately be given a chance to talk over his fears. If this is not enough, and if explanation does not relieve him, hypnosis or intoxication with amytal, pentothal or evipal may be necessary to aid the patient to recall and relive the dreadful experiences which are upsetting him.⁵ Alcohol or light anesthesia may be used, but the standard technic is the administration of $7\frac{1}{2}$ grains (0.5 Gm.) of sodium amytal intravenously. This is given slowly, so that the patient at first becomes euphoric and loquacious, perhaps telling of important repressed experiences and often, then and there, overcoming motor or sensory symptoms. Later he sleeps and may awake relieved. Hypnosis is sometimes useful early in patients with hysterical conversion symptoms.

If these emergency methods do not work immediately the psychiatrist must begin with more prolonged methods, such as those employed in

5. Miller,¹ appendix D.

civil practice. Psychoanalysis is impossible under war conditions, but the knowledge of human reactions attained by a sound psychoanalytic training can be of great use in applying shorter forms of psychotherapy. The important thing is for the physician to obtain a sympathetic rapport with the patient, so that he can go into the traumatic episode and clear up the amnesias step by step. Reeducation and occupation are important. Back-slapping reassurance, persuasion and exhortation are as useless as the discarded ordeals of faradic pain too popular in the last war.

ELECTRIC SHOCK THERAPY FOR PSYCHOSES

The use of electricity in neurology and psychiatry is over one hundred years old, but the delivery of strong electric shock to the brain is a relatively new procedure. Bini,⁶ in 1938, used such treatment in Italy. He took up "electroshock" because he wished to cause convulsions without the disagreeable and traumatic effects often accompanying metrazol fits. In this he seems to have had some success. The method was taken up on the Continent and in England, and later in the United States. Gonda⁷ reviews the literature in a recent paper and describes the method and the results. To my mind he paints too rosy a picture and minimizes the risks. The convulsions are severe and may cause fractures. The picture is usually as follows: When the switch is thrown, the patient is apparently knocked unconscious and goes into an instantaneous muscular spasm like that of an animal whose motor cortex has been strongly stimulated. There is then an interval of a few seconds before the convulsion proper starts. The patient turns pale, the pupils dilate and the eyes deviate upward. Then, with a cry, the patient goes into extensor spasm, arching the back and holding a rigid posture. Breathing stops and the patient grows cyanotic. Then the spasm is interrupted, so that clonic jerks become more and more frequent and severe. After thirty to sixty seconds the convulsive movements cease and the patient lies limp. Three or four minutes later the patient begins to make aimless movements and look about in a confused way; for five to ten minutes more he may remain semiconscious and may behave as if terrified. The confused period may end with sudden awakening and a surprised expression, or the patient may remain somewhat confused for hours. Apparently the amnesia caused by suddenly being knocked unconscious is both retrograde and antigrade, for the patient has no unpleasant memory of the experience. On the whole the fits are more severe than clinical grand mal.

6. Bini, L.: Experimental Researches on Epileptic Attacks Induced by Electric Current, *Am. J. Psychiat.* **94**:172, 1938.

7. Gonda, V. E.: Treatment of Mental Disorders with Electrically Induced Convulsions, *Dis. Nerv. System* **2**:84, 1941.

Such an episode would seem to me severe enough to require hospitalization. With this some electrotherapeutists⁸ do not agree, believing that the procedure may be applied to outpatients if several hours are allotted for preparation and observation after the shock.

Just what takes place in the brain as a result of these electric shocks is not known. The histologic effect of electric currents of various kinds and strengths has of course been studied,⁹ but studies on animals with currents comparable to those used for therapeutic shocks are few and poorly reported. Some of the workers briefly state that animal work was done and showed no lesions. Such reports are not convincing because sufficient data are not given about number of animals, histologic technic and controls. Recent work by Alpers and Hughes¹⁰ is carefully reported: A group of 15 cats, each of which had ten threshold shocks (i. e., just enough to cause convulsion) showed ten subarachnoid hemorrhages and eight cerebral hemorrhages. Another group of 15 cats in a more prolonged experiment showed four hemorrhages and four chronic cerebral lesions. Heilbrunn and Liebert¹¹ took biopsy specimens from the brains of rabbits at short intervals for several hours after electric shock. All the early specimens showed changes in the nerve cells, but one and a half hours after the shock many cells had returned to normal. This is important evidence but should be amplified. Added to this is the electroencephalographic evidence of damage to the brain lasting for weeks or months. Grinker, Levy and Serota¹² found abnormal waves developing after electric shock in 5 of 12 patients; these 5 and 3 more also showed mental disturbances in which the higher intellectual functions were conspicuously affected; i. e., the patients showed a "slap happy" state of euphoria. Both the clinical psychologic disturbances and the abnormal brain waves were at their worst in the first weeks after shock and gradually improved, indicating reversible lesions, like those described in the biopsy experiments on rabbits. Sufficiently long observations, however, have not been made to say whether or not

8. Myerson, A.: Experience with Electric-Shock Therapy in Mental Disease, *New England J. Med.* **224**:1081, 1941.

9. Morrison, L. R.; Weeks, A., and Cobb, S.: Histopathology of Different Types of Electric Shock on Mammalian Brains, *J. Indust. Hyg.* **12**:324, 1930. Weeks, A. W., and Alexander, L.: Distribution of Electric Current in Animal Body: Experimental Investigation of Sixty Cycle Alternating Current, *J. Indust. Hyg. & Toxicol.* **21**:517, 1939.

10. Alpers, B., and Hughes, J.: The Brain Changes in Electrically Induced Convulsions in Cats, *Arch. Neurol. & Psychiat.*, to be published.

11. Heilbrunn, G., and Liebert, E.: Biopsies on the Brain Following Artificially Produced Convulsions, *Arch. Neurol. & Psychiat.* **46**:548 (Sept.) 1941.

12. Grinker, R. R.; Levy, N. A., and Serota, H. M.: Electroencephalographic and Clinical Studies Following Metrazol and Electrically Induced Convulsive Therapy of Affective Disorders, *Arch. Neurol. & Psychiat.* **46**:542 (Sept.) 1941.

any permanent disorder remains. A few cases are coming to notice in which epilepsy seems to have been started. Probably an electroencephalogram should be made in each case before shock treatment to rule out latent or "subclinical" epilepsy.

My own opinion is that a convulsion is an extremely severe symptom and always indicates cerebral injury whether it is "spontaneous" or is "therapeutically" induced. I believe that electric shock is less dangerous than metrazol but is to be classified as one of the destructive forms of therapy. As a physician who believes that good therapy consists in conserving rather than injuring the organism, I look with alarm at the rapid spread of electric shock therapy and believe that it should be tried out for a year or two longer by careful workers trained in physics and electrophysiology, before the shocking machines are put into the hands of therapists not so trained. The psychiatrist who cares for patients during prolonged depressions has great responsibility and a wearisome and often thankless task; so the temptation to do something and try something new is often great. The question is whether such treatments are justified.

So far the results in states of depression are encouraging. In schizophrenia and neurosis they are poor. Gonda⁷ reports 11 patients with depression, 10 of whom recovered. Of his 29 schizophrenic patients, 17 showed "complete remission" and 6 improved. It is important to note however, that these patients were in the early stage of the disease, most of them with symptoms of less than a year's duration. The remission rate for such patients in the smaller hospitals with adequate staff and equipment—using no shock therapy, is practically as high. Myerson⁸ shows clearly that depressive states are the ones most benefited by electric shock. Of his 24 depressed patients 17 showed remission or marked improvement. None of his 9 schizophrenic patients was significantly benefited, nor were 3 patients with chronic neurosis.

At the meeting of the American Psychiatric Association at Richmond, Va., in June 1941, eight hospitals combined their results and gave a demonstration to show that electroshock therapy had advantages over other radical procedures, being more acceptable to the patient, easier to administer by the physician, productive of fewer fractures (5 per cent) and less expensive. Standard electric shocks given to animals were found to cause hemorrhages in the cortex and the arachnoid. The therapeutic results can be tabulated as follows:

Condition	Number of Patients			
	Treated	Recovered	Improved	Not Improved
Involutional melancholia.....	76	55	14	7
Manic-depressive, manic.....	29	16	5	8
Manic-depressive, depressed.....	106	79	11	16
Schizophrenia.....	119	25	31	63

In evaluating these figures it must be remembered that most manic-depressive patients recover spontaneously and many of those with early schizophrenia have remissions. The remarkable and hopeful data are those in the cases of involutional melancholia.

As I just indicated, my objections to electroshock therapy are not against the method *per se*. The results show that it has some value. My fear is that the method is spreading too rapidly, that accidents may occur and that damage may be done to many brains before psychiatrists are aware of the risks. Already the commercial aspect is becoming prominent, and many machines are on the market. Some of these are not reliable, and some of the salesmen make the method seem ridiculously simple. Well trained electrical engineers have been astonished at the magnitude of the shocks given and at the faulty machines used; for example, some therapists rely on apparatus with inaccurate timing and erroneous measurement of current. One physicist who has looked into the matter reports that the commercial machines seem to be at fault in one or more of the following ways:

(a) The timer depends either on the properties of electronic circuits or on various kinds of "time delay" relays. These methods are not adequate for timing very short intervals (tenth seconds). To be thoroughly reliable the timer should consist of a mechanical switching mechanism driven by a synchronous motor of ample power.

(b) Current regulation is attempted indirectly by applying a regulated voltage to a supposedly known resistance. Actually the skull does not represent a simple ohmic resistance but is complicated by capacitive and polarization effects. Furthermore, there may be a difference of several hundred per cent between the resistance as measured immediately before the treatment and the resistance that obtains during the brief interval the current is passing through the skull and brain. In short, it is *not* possible to regulate the dosage (current) by regulating the applied voltage. What is needed is a device that will regulate current directly, independent of resistance. Measuring the resistance is then not necessary so far as the treatment current is concerned, but it is nevertheless advisable to do so just before giving the shock, to make sure that all the connections in the circuit, including those on the scalp, are in good contact.

(c) Current flow during the shock treatment is supposed to be measured on some machines by ordinary ammeters. This is impossible during the brief shocks used, and many of the data published concerning amperage of current administered to patients are therefore worthless. Brief currents can be measured by some form of recording oscillograph. However, an alternative method is to make the current flow

first through a "dummy" patient, when it can be measured at leisure with an ammeter, and then transfer it without change to the patient for a brief interval. This method has the important advantage that the current is known before the treatment.

(d) Using current regulation (as indicated in *b*), rather than voltage regulation, requires some form of control to prevent excessive voltage from ever developing across the output terminals in case of faulty connections.

A shock therapy apparatus embodying these principles ought to give reliable data and should be safe, in the sense that the time and current dose may be adjusted beforehand with the assurance that the patient will receive just this intended dose. Guillemin¹³ has designed an apparatus of this type, now in use at the McLean Hospital, Belmont, Mass.

APHASIA

During recent years Ingham, Nielsen and von Hagen, in Los Angeles, have taken an especial interest in aphasia and have collected and carefully studied a large number of cases. These have been frequently reported in the *Bulletin of the Los Angeles Neurological Society* and have resulted in two longer contributions by Nielsen¹⁴ which are a great aid to the neurologist in understanding disturbances of language and allied disorders of cerebral function. No short summary of these disorders can be adequate and accurate because they comprise the difficult field where neurology meets psychiatry and physiology is taken over by psychology. In short, integration reaches a state of such complexity that neural impulses arouse meaningful and symbolic reactions. The levels of reflex and racial reactions are surpassed, and learned skills that are cerebrally localized in a leading hemisphere are attained. Among these skills is language.

Nielsen's contribution lies in organizing the classic data of such authorities as Jackson, Henschen, Goldstein and Foerster and in adding to these data new cases which fill in the gaps in evidence and explain the discrepancies. The crucial new facts have come from the neurosurgeons and their observations on the effects of cerebral lobectomy and stimulation.

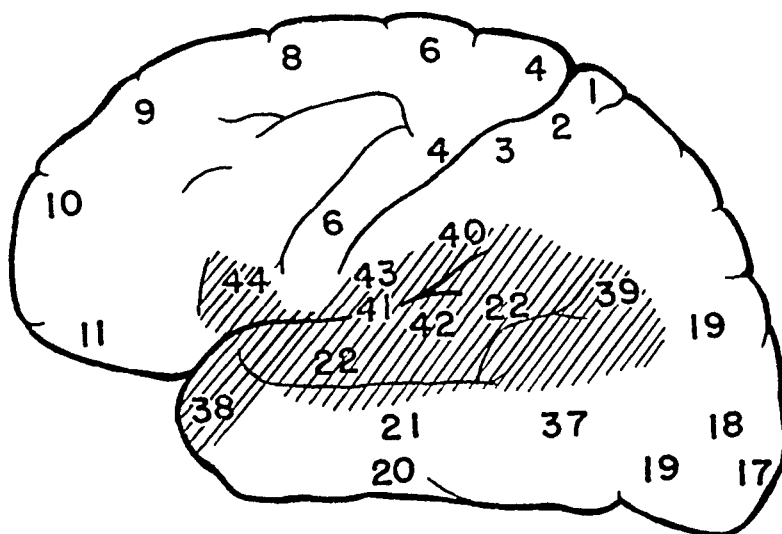
The senses important to language are vision and hearing (sense of touch replaces vision for blind people reading Braille, but it is secondary for normal people). The two main senses each have three levels of

13. Guillemin, V.: Personal communication to the author.

14. Nielsen, J. M.: *A Textbook of Clinical Neurology*, New York, Paul B. Hoeber, Inc., 1941; *Agnosia, Apraxia, Aphasia*, Los Angeles, Los Angeles Neurological Society, 1936.

integration. Visual perception is localized in area 17 (fig.), visual recognition in area 18 and revisualization in parts of area 19. A lesion at the first level causes blindness at the second, loss of recognition (the patient does not know what the perceived object means; hence he has visual agnosia). A lesion in area 19 causes loss of power to revisualize scenes or persons. The patient cannot remember the plan of a house and cannot get home even though he may recognize the street or house he is seeing at the moment. He is visually disoriented because he cannot bring back series of pictures.

The auditory sense has three levels, not so clearly defined. The first level is not in the cortex; primary auditory perception is in the mesial geniculate bodies of the thalami. Each cochlea sends fibers to both geniculate bodies. Thence fibers go to the temporal lobes, where



A diagram of the left cerebral hemisphere showing the location of histologically recognizable areas (after Brodmann). The shaded zone includes areas involved in language. Areas 4 and 41 lie largely in the depths of the fissures.

cortical areas 41 and 42 make the center for auditory recognition (level 2). Since the innervation is bilateral, a single cerebral lesion cannot cause complete agnosia, and even bilateral lesions never cause deafness. Acoustic agnosia for sounds is not known to occur without acoustic verbal agnosia, but in many cases of the latter the recognition for sounds is retained. For example, a patient may have lost his knowledge of the meaning of word symbols but can still recognize a whistle, the sound of crumpling paper, etc., and say what is going on. Thus it is obvious that the acoustic mechanism is more concentrated in space in each temporal lobe but has less unilaterality in the dominant hemisphere than is the case with the visual mechanism.

Recognition of learned symbols has been mentioned in respect to words heard; for words seen the center is in the angular gyrus, area 39,

and a lesion here causes visual verbal agnosia, or "word blindness," as opposed to the "word deafness" resulting from a lesion in the temporal lobe.

So much for a brief description of the most important points concerning the receiving end of linguistic disorder, the "sensory aphasia" of older authors. The motor side is equally complex and depends on an understanding of the fact that no learned motor skill can be practiced without an ideational plan. This is a psychic elaboration necessary as a precursor to the carrying out of any complex motor act. This ideational planning is called *eupraxia*; the normal person knows how to do a thing quickly and almost automatically when requested. A defect of such performance in response to command is *apraxia*. It is a symptom of injury to the sensorimotor elaboration areas of the cortex, corresponding to agnosia from a lesion in the more strictly sensory area. In relation to most performances *eupraxia* is bilateral, the acts of one hand, for example, being planned in the opposite precentral and supramarginal gyri. Lesions of these areas (parts of 6 and 40) or their fiber connections may cause *apraxia*.

Apraxia of the organs of speech (tongue, lips, larynx) causes "motor aphasia"; the patient loses the memory of how to make the movements to articulate words; he may know just what he wants to say, but he cannot get the plan of the word into his mind. A lesion of Broca's area (44) causes this symptom. Much controversy once raged over "Broca's aphasia," but Nielsen's summarizing of the data, including that from modern surgical procedures, leaves no doubt that motor aphasia has this precise localization. The cases that seemed to disprove it are probably cases in which area 44 of the minor side took over the function of motor speech readily; i. e., the patients were somewhat ambidextrous. Moreover, expletive speech is always possible with the minor side; only propositional speech is lost when the major area 44 is injured. In other words, the function of language is largely concentrated in the leading hemisphere, but a primitive sort of speech (emotional, expletive, habitual) is subserved in the homologous areas of the minor hemisphere. Areas 39, 44, 19, 18 and 17 are the most unilateral in function, in that order. Areas 41 and 42 are less unilateral. Individual variation in relation to the degree of handedness is important.

The last point, of the many good ones emphasized by Nielsen, to which I wish to call attention is the following: Area 39 has the function of symbolic visual recognition, i. e., understanding letters and words by sight. Because words were first learned by hearing, however, area 39 cannot function if cut off from areas 41 and 42. During the process of learning to read, words are sounded out or told to one. Thus the portion of the temporal lobe lying between areas 39 and 42 is of great

importance. This takes in the posterior part of area 22 and the upper part of area 37. A lesion here may cause as much loss of reading ability (alexia) as a lesion directly in area 39. Moreover, because language is learned by associating vision and hearing with objects and symbols, this area is particularly important. In fact, Nielsen calls it "the language formation area."

Take, for example, the case of objective nouns, the simplest and commonest words used. They are names, usually of objects seen. So engrams must be stored in areas 22 and 37 correlating both visual and auditory meanings. That this is true is shown by cases of temporal lobectomy in which the language formation area of the leading hemisphere is removed. The result is amnesic aphasia. The patient has lost the storage mechanism for nouns; his "naming center" is gone. When shown a pen, he uses circumlocution and may reply "It's to write with" but cannot say "pen." He is suffering from the symptom of anomia, one of the commonest subdivisions of aphasia. It is, in a way, the opposite of motor aphasia.

If one takes these main symptoms (which are well explained physiologically), agnosia, motor aphasia and anomia, and adds the obvious complications, it is seen that many special sorts of aphasia are possible. But by sticking to the principles laid down, these strange phenomena can largely be explained and localized. For example, one can hear music as well as words; therefore "amusia" is found. One can learn several languages and have marked aphasia in one but little in another. Symbols used for mathematics are different from letters; so one may have agnosia for figures. In fact, loss of the ability to calculate is found after lesions in various areas and is not well understood. Semantic aphasia, a term coined by Head, should be mentioned because it is the commonest of all aphasias and is not localizable. It consists of a quantitative reduction in the capacity for and comprehension of speech. The victim has a little of all language functions left but cannot put sentences together or express any complex idea. This phenomenon is present in persons with diffuse cerebral lesions commonly senile, in toxic patients and in normal but excessively fatigued persons. In fact, almost all patients with aphasia have an element of the semantic form, and careful examination will usually show some mental loss. Semantic aphasia is a form of dementia.

The complexity of the subject of aphasia, apraxia and agnosia (symbolization) is remarkable but fascinating. Many volumes have been written on it, and many physicians shun the study of language because it seems hopelessly complicated. One is grateful to Nielsen for a reasonable simplification.

Any mention of aphasia brings to mind the name of Henry Head. He was one of the leading neurologists of this generation; born on Aug. 5, 1861, he had long training both in England and in Europe. His leadership in the medical world was indicated by his holding the editorship of *Brain* from 1905 to 1922. During the first World War he was especially interested in the effects of injuries of the brain and wrote a monograph on aphasia which was the result of many years' study and follow-up observation of these war wounds. He died on Oct. 9, 1940, after suffering for almost eighteen years with slowly progressive paralysis agitans. He was a man of broad interests, many accomplishments and much fortitude.

THE NEUROLOGIC APPROACH TO MENTAL DISORDER

In his presidential address to the Section of Psychiatry of the Royal Society of Medicine in March 1941, Symonds¹⁵ spoke on the subject used as a heading for these paragraphs. His logic is so sound and his examples so well chosen that I wish to express my enthusiasm for his point of view and give one quotation. During recent years there has been too much specializing, and specializing within specialties. In neuro-psychiatry this has led to the practice of psychotherapy by persons who know nothing of the brain. Psychiatry has been narrowly defined by some as the study of interpersonal relationships. Others consider that "organic neurology" can be separated from psychiatry and psychology. In regard to "medical psychology" (in this country the psychotherapy practiced by clinical psychologists), Symonds says:

The medical psychologist also asserts that for his purpose training in neurology is unnecessary. He may be prepared to admit that all mental activity has its physical basis, and that brain is the organ of mind, but these propositions are, for him, of theoretical value only. They have no real bearing upon the practical diagnosis and treatment of the neuroses. An approach to these problems in terms of neurophysiology and neuropathology may be an interesting intellectual exercise, but has no practical significance. I have already attempted to indicate the fallacies in such argument, with especial reference to the affective disorders. I would take as another example the diagnosis and treatment of neurosis following head injury. Here we have a patient whose adjustments to inner need and external stimulus are faulty. How far is this due to inherited disposition, training, experience, present needs and difficulties; how far to the nature and situation of cerebral damage? Is the cerebral injury of reversible or irreversible character? If there is headache, how much is due to meningeal adhesion, alterations in the cerebrospinal fluid pressure or circulation, or disordered cortical rhythm? How much to fear, depression, or defeatism arising from difficulty in coping with the situation as a whole? If there is insomnia, how much is due to anxiety, how much to hypothalamic damage? I submit that the answers to some of these questions are impossible without

15. Symonds, C.: The Neurological Approach to Mental Disorder, Proc. Roy. Soc. Med. **34**:289, 1941.

neurological training, and that unless they are all answered diagnosis and treatment must be at fault. I do not think this is an unfair example. There are many other instances in which knowledge of cerebral function in health and disease in relation to nutrition—including vitamin supply, effect of drugs, endocrine disorder, or oxygen need—is essential to the proper understanding and treatment of neurosis. . . .

Looking to the past I believe that neurology and psychiatry in this country were kept apart at first, because the neurologist was interested in morbid anatomy, and the psychiatrist in the care of the insane. . . . At present the gap is narrower than it has ever been. The fruits of recent research and experiment have emphasized common interest, for example the work of Bard and others on hypothalamic function, the contribution of the biochemists to the understanding of brain metabolism, the study of cortical rhythm by the electro-encephalogram, the lessons of continuous narcosis and convulsive therapy. Looking to the future I believe that the merging of the two specialties into one is not only desirable but inevitable.

Book Reviews

The Modern Treatment of Syphilis. By J. E. Moore, M.D., Associate Professor of Medicine, the Johns Hopkins University, with the collaboration of J. E. Kemp, M.D.; H. Eagle, M.D.; P. Padget, M.D., and M. S. Goodwin, M.D. Second edition. Price, \$7. Pp. XII + 674, with 98 figures and 122 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The first edition of this book appeared in 1933. The reviews which it received are worth mentioning for they are so remarkably uncomplaining. The *Archives of Dermatology and Syphilology* (30:330 [Aug.] 1934) called the book a great one and a real contribution to the knowledge of syphilis. The *Journal of the American Medical Association* (102:1328 [April 21] 1934) termed it a classic and prophesied many future editions. The *ARCHIVES* (53:632 [April] 1934), so likely to be conservative and uneffusive, fairly outdid itself: "From time to time books appear which start out as landmarks in a subject so far as they rid themselves of the deadwood of tradition and by a consideration of actual facts formulate definitely a new point of view. Such a result, in our opinion, has been achieved by Moore in his discussion of the modern treatment of syphilis."

The second edition is 139 pages longer than the first edition and is not only more ample but better in every way. It is up to date; it is better illustrated; the tabulations are easier to understand; the language continues readable and easy to follow, and the bibliography has grown as a clever gardener allows a hedge to grow—by a wise combination of pruning and fresh planting. Thus the bibliography is not much longer than it was but a good deal broader by virtue of useful additions and wise deletions. There are two entirely new chapters which add to the effectiveness of the volume as a whole, one on the public health aspects of syphilis and the other dealing with the matter of intensive arsenic therapy.

The book is sure to be successful. Successful books, like successful doctors, are worth cultivating. Medical students and physicians are advised to introduce themselves to this book at once in order to become thoroughly acquainted with the modern treatment of an old and important disease.

Preeclamptic and Eclamptic Toxemia of Pregnancy. By Lewis Dexter and Soma Weiss. Pp. 415, with 44 figures. Boston: Little, Brown & Co., 1941.

No subject in medicine has been in a greater state of confusion than the "toxemias of pregnancy," encrusted by traditions often of almost medieval antiquity and studied for the most part by men not trained in the proper methods. Real light seems now to have come from the careful studies of Dexter and Weiss. Here, for the first time, the reviewer finds a really intelligible and satisfying account of these puzzling disorders, made possible mainly by the training of the authors in vascular and renal disease. Clinical features, pathophysiologic aspects and anatomic lesions are all correlated, and each chapter is followed by liberal bibliography. Useful charts illustrate the case reports.

The Essentials of Occupational Diseases. By Jewett V. Reed and A. K. Harcourt. Price, \$4.50. Pp. 225, octavo. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This book seems admirably designed to orient the physician in the essentials of occupational disease. A long list of chemical poisons and their effects, concisely discussed in alphabetic order, is followed by material on physical agents, the cutaneous lesions of occupational disease, silicosis, malignant disease associated with occupation and, finally, occupational disease due to infection. A well selected bibliography covers 10 pages.

INDEX TO VOLUME 68

Book Reviews are grouped together and are indexed under that heading in alphabetical order under the letter B.

Abdomen: See also Gastrointestinal Tract
cause of so-called side ache that occurs in normal persons; personal observations, 94

Abnormalities and Deformities: See under names of organs and regions, as Ribs; etc.

Abscess: See under names of organs and regions

Acacia: See Nephritis

Acetone: See Blood, ketone bodies

Acidosis, efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066

Acrocyanosis: See Cyanosis

Acromegaly and diabetes, 148

Acropachyderma: See Extremities

Acrosclerosis: See Scleroderma

Addison's Disease, abnormal function of kidney in, 984
carbohydrate metabolism in, 991
changes in body fluids in, 985
diagnosis of, 1000
diseases of adrenal glands, 979
electrolyte metabolism, 981
pathology of, 980
treatment of, 1004

Adrenal Preparations, adrenal cortical substances, 997
adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105

Adrenals; adrenal cortical hyperplasia, 1019
diseases of adrenal glands; Addison's disease, 979
diseases of adrenal glands; tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances, 1010
diseases of adrenal medulla, 1032
medullary hyperadrenalism, 1033
tumors of adrenal cortex, 1010

Age, Old: See Old Age

Ainhum, 621

Air, sterilization of, 367

Air Passages: See Respiratory Tract

Air Raids, shelter legs, 622

Allergy: See Anaphylaxis and Allergy

Altschule, M. D.: Acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957

Amputation, 658

Amylase in Blood: See under Blood

Amyloidosis, hepatic function in patients with, 309

Anaphylaxis and Allergy, immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25

Andrus, W. DeW.: Differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1,4-naphthoquinone) as diagnostic aid, 199

Anemia, acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957

Anemia—Continued

"primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042

Anesthesia, paravertebral block, 636

Aneurysm, 644

Angioma, tumors of blood and lymph vessels, 615

Animals, unusual infections contracted from animals, 360

Aphasia, 1240

Appendicitis; review of literature, 821

Arteries: See also Aneurysm; Arteriosclerosis; Blood pressure; Blood, vessels; Embolism; Periarthritis; Thrombosis; etc.
inflammation; arteritis, 615
multiple fresh coronary occlusions in patients with antecedent shock, 181
oscillometry, 610

Arteriosclerosis, 610
primary pulmonary vascular sclerosis, 560

Arteritis: See Arteries, inflammation

Arthritis, 354
and circulation, 617
serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18

Bacilli: See Bacteria

Bacillus Friedländeri: See Bacteria, mucosus capsulatus group

Bacteremia, significance of bacteremia caused by Staphylococcus aureus; study of 122 cases and review of literature concerned with experimental infection in animals, 851

Bacteria: See also Staphylococci; Streptococci; Viruses; etc.
abortus and melitense group; brucellosis, 351
abortus and melitense group; chemotherapy of bacillary infection, 333
infection caused by Bacillus violaceus, 353
mucosus capsulatus group; Friedländer pneumonia, 348
Shigella: See Dysentery
Tularensis: See Tularemia

Bacteriophage, 367

Bancroft, P. M.: Elliptic erythrocytes in man, 1043

Bashour, J. T.: Chemical factors in formation of gallstones, 1037

Bauman, E.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102

Bauman, L.: Chemical factors in formation of gallstones, 1037

Bennett, R. H.: Treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121

Berk, J. E.: Diagnosis of carcinoma of pancreas, 525

Bilden, E.: Determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740

Biliary Tract: See Gallbladder; Liver

Binger, M. W.: Acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513

- Block, W. D.: Serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
- Blood: See also Erythrocytes; Leukocytes
 acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
 adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
 Circulation: See also Arteries; Capillaries; Heart; Veins; etc.
 circulation and arthritis, 617
 coagulation; differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1,4-naphthoquinone) as diagnostic aid, 199
 direct cultivation of *Bacterium tularensis* from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
 Diseases: See Anemia; etc.
 fats and lipoids; serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
 fusospirochetosis; recovery of causative organisms from blood with report of 2 cases, 80
 ketone bodies; origin from fats and their regulation, 674
 origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
 picture in chickenpox, 294
 pigment; acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
 pressure, abnormalities of, 625
 pressure; exercise test, 622
 pressure, high; adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
 pressure, high; state of motor centers in circulatory insufficiency, 498
 pressure, high; studies on "essential" hypertension; association of hypertension with organic renal disease, 261
 pressure, high; surgical treatment of hypertension, 653
 pressure, low; hypotension, 635
 pressure studies on West Indians and Panamanians living on Isthmus of Panama, 466
 response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
 sugar in case of complete hypophysectomy, 893
 sugar; metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
 sugar; metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
 Vessels: See also Arteries; Capillaries; Periarthritis; Veins; etc.
 vessels; vasospastic disorders, 619
- Blumgart, H. L.: Multiple fresh coronary occlusions in patients with antecedent shock, 181
- Body Fluids: See Fluids
- Bones, acropachyderma with pachyperiostitis; report of case, 687

BOOK REVIEWS:

- Age Morphology of Primary Tubercles; H. Sweeney, 180
 Annual Review of Physiology; J. M. Luck and V. E. Hall, 374

BOOK REVIEWS—Continued

- Avitaminoses; W. H. Eddy and G. Dollendorf, 850
 Bacillary and Rickettsial Infections; W. H. Holmes, 177
 Biologie der Grosstadt; B. de Rudder and F. Linke, 180
 Biology of Laboratory Mouse; edited by G. D. Snell, 373
 Cardiac Clinica; F. A. Willius, 1041
 Cardiologia (Cardiology); J. M. Hoyos, 179
 Clinical Immunology, Biotherapy and Chemotherapy in Diagnosis, Prevention and Treatment of Disease; J. A. Kolmer and L. Tuft, 1040
 Clinical Pellagra; S. Harris, 370
 Diabetic Manual; E. P. Joslin, 662
 Dietetics for Clinician; M. A. Bridges, 850
 Diseases of Digestive System; S. A. Portis, 371
 Diseases of Nails; V. Pardo-Castello, 1041
 Doctor and Difficult Child; W. Moodie, 372
 Electrocardiography in Practice; A. Graybiel and P. D. White, 371
 Enfermedades del riñon (Diseases of Kidneys); J. M. Hoyos, 370
 Essentials of Occupational Diseases; J. V. Reed and A. K. Harcourt, 1246
 Frank Howard Lahey: Birthday Volume by various authors and sponsors, 371
 Handbook of Communicable Diseases; F. H. Top and others, 1041
 Hemorrhagic Diseases; K. K. Nygaard, 178
 Herzkrankheiten: I. Physiologie, Beurteilung und funktionelle Pathologie des Herzens; M. Hochrein, 180
 Hypertonie und Sklerose der Blutstrombahn; F. Lange, 1042
 Lymphatics, Lymph and Lymphoid Tissue: Their Physiological and Clinical Significance; C. K. Drinker and J. M. Yoffey, 1040
 Man's Greatest Victory Over Tuberculosis; J. A. Myers, 374
 Manual of Physical Diagnosis; M. Lewison, E. B. Frelich and G. C. Coe, 372
 March of Medicine, 849
 Medical Aspects of Boxing; E. Jokl, 662
 Microbes Which Help to Destroy Us; P. W. Allen, D. F. Holtman and L. A. McBee, 1042
 Modern Treatment of Syphilis; J. E. Moore and others, 1246
 Objective and Experimental Psychiatry; D. E. Cameron, 1040
 Physical Medicine; F. H. Krusen, 848
 Preeclamptic and Eclamptic Toxemia of Pregnancy; L. Dexter and S. Weiss, 1246
 Radiologic Physics; C. Weyl, S. R. Warren Jr. and D. B. O'Neill, 847
 Role of Liver in Surgery; F. F. Boyce, 180
 Story of Clinical Pulmonary Tuberculosis; L. Brown, 372
 Symposium on Blood and Blood-Forming Organs, 178
 Synopsis of Applied Pathological Chemistry; J. E. Andes and A. G. Eaton, 1041
 Synopsis of Diseases of Heart and Arteries; G. R. Herrmann, 847
 Textbook of Ophthalmology; S. R. Gifford, 850
 Textbook of Pediatrics; J. P. C. Griffith and A. G. Mitchell, 849
 Tratado de quimica normal y patologica de la sangre; L. Corona, 179
 Ueber die Häufigkeit von Krankheiten: Tuberkulose, Ulkuskrankheit und Krebs; F. Reichert, 849
 Vitamins K; H. R. Butt and A. M. Snell, 662
- Brain: See Nervous System; etc.
 Diseases: See Encephalitis
 Bright's Disease: See Nephritis
 Brill, I. C.: Primary pulmonary vascular sclerosis, 560
 Bronchiectasis, natural history of; clinical, roentgenologic and pathologic study, 395
 Bronchiolitis: See Bronchitis
 Bronchitis, bronchiolitis fibrosa obliterans; report of case, 663

- Brown, E.: Efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
- Brugsch, H. G.: Acropachyderma with pachyperiostitis; report of case, 687
- Buchanan, O. H.: Serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
- Butt, E. M.: Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
- Cancer:** See under names of organs and regions, as Pancreas; etc.
- Capillaries, 602. See also Blood, vessels
- Capps, R. B.: Cause of so-called side ache that occurs in normal persons; personal observations, 94
- Carbohydrates: See also Dextrose; Glycogen; etc.
glycogen and carbohydrate metabolism, 134
metabolism in Addison's disease, 991
metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
vitamin deficiency and metabolism of, 153
- Cardiovascular Diseases: See Blood vessels; Heart
- Cardiovascular System: See Arteries; Blood vessels; Heart; etc.
- Carotene and vitamin A content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
- Carotid Sinus syndrome, 647
- Chagas' Disease: See Trypanosomiasis
- Chemotherapy: See under names of diseases, as Endocarditis; Influenza; Meningitis; Pneumonia; etc.
- Chickenpox, blood picture in, 294
- Chill, clinical and physiologic characteristics of, 241
- Cholelithiasis: See Gallbladder, calculi
- Choriomeningitis: See Meningitis
- Cobb, S.: Review of neuropsychiatry for 1941, 1232
- Coccidioidosis, pulmonary cavitation associated with coccidioidal infection, 1179
- Cohen, S. E.: Hepatic function in patients with amyloidosis, 309
- Cold, effect on extremities, 606
- Coma: See Diabetes Mellitus
- Communicable Diseases: See also Meningitis; Syphilis; etc.
infectious diseases; review of significant publications in 1940-1941, 325
therapy with sulfanilamide and its derivatives, 325
- Conn, E. S.: Metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
Metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
Metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
- Conn, J. W.: Metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
Metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
Metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
- Consolazio, W. V.: Hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
- Cowpox, milkers' nodules, 360
- Cyanosis; acrocyanosis, 620
- Cysts: See under names of organs and regions
- Dameshek, W.: "Primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
- Davis, L.: Pinealectomies on young mammals, 176
- Deficiency Diseases: See also Diet and Dietetics; Nutrition; Vitamins; etc.
review of literature, 837
- Dementia Praecox, hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
- de Takáts, G.: Critical review of surgical treatment of vascular diseases, 636
- Vascular diseases; seventh annual review, 599
- Dextrose: See also Blood, sugar; Carbohydrates; etc.
tolerance test; importance in diagnosis of marginal malnutrition, 945
- Diabetes Insipidus and antidiuretic principle of posterior lobe of pituitary gland, 170
and diabetes mellitus, 149
- Diabetes Mellitus: See also Blood sugar
and acromegaly, 148
and diabetes insipidus, 149
and metabolism; review of certain recent contributions, 134
and ocular conditions and neuritis, 152
and pancreatic lesions, 149
and vascular disease, 151
associated with pregnancy, 142
diabetic coma, 151
diabetogenic action of extracts of anterior lobe of pituitary gland, 166
diagnosis, 141
diet in, 154
efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
incidence and mortality, 138
juvenile, 147
miscellaneous acute complications and diabetic coma, 149
pancreas and organs of secretion, 147
traumatic factors, 141
vitamin deficiency and metabolism of carbohydrate, 153
- Diatheses, hemorrhagic; analysis of 355 autopsy reports, 112
- Diet and Dietetics: See also Nutrition; Vitamins; etc.
metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
- Digestive Tract: See Gastrointestinal Tract; Intestines; Stomach; etc.
- Diuresis and Diuretics: See also Diabetes Insipidus; Kidneys
diabetes insipidus and antidiuretic principle of posterior lobe of pituitary gland, 170
- Donath-Landsteiner Phenomenon: See Hemoglobinuria
- Dozzi, D. L.: Origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
- Drugs, effect on extremities, 608
- Duodenum, Ulcers: See Peptic Ulcer
- Dysentery, bacillary, 350
- Eagle, H.: Biologic false positive serologic reactions in tests for syphilis; occurrence in normal persons, 898
Biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
- Ebert, R. V.: Response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
- Ecthyma contagiosum, 360
- Edema: See Kidneys
- Electrocardiogram: See under Heart
- Electrolytes, metabolism in Addison's disease, 981
- Embolism: See also Thrombosis
and thrombosis, 612
arterial occlusions, 641
therapy, 623

- Embolism**—Continued
 thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
 venous occlusions, 638
- Encephalitis, equine**, 359
- Endocarditis**, chemotherapy of subacute bacterial endocarditis, 331
- Endocrine Glands**, pancreas and organs of secretion in diabetes mellitus, 147
- Energy Exchange**: See Metabolism
- Enzer, N.**: State of motor centers in circulatory insufficiency, 498
- Enzymes**, bactericidal, 366
- Epinephrine**: See Adrenal Preparations
- Epstein, E. Z.**: Rheumatic pneumonia, 1074
- Erythrocytes**: See also Anemia; etc.
 elliptic, in man, 1043
 production; transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
- Erythropoiesis**: See Erythrocytes, production
- Esophagus**, diseases; review of literature, 788
- Exercise**, cause of so-called side ache that occurs in normal persons; personal observations, 94
 tests, 622
- Extremities**, acropachyderma with pachyperostitis; report of case, 687
 blood flow, 599
 Blood Supply: See also Blood vessels; Embolism; Raynaud's Disease; Thromboangitis obliterans; etc.
 blood supply; critical review of surgical treatment of vascular diseases, 636
 blood supply; sympathectomy in treatment of peripheral circulatory disturbances, 649
 blood supply; vascular diseases; seventh annual review, 599
 effect of cold on, 606
 effect of drugs on, 608
 Paralysis: See Poliomyelitis
 vascular disease and diabetes, 151
- Eyes**, diabetes and ocular conditions and neuritis, 152
- Fat**, origin of ketone bodies from fats and their regulation, 674
- Fatigue**, state of motor centers in circulatory insufficiency, 498
- Favre-Nicolas' Disease**: See Lymphogranuloma Venereum
- Feces**, determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
- Fever**: See Typhoid; etc.
- Fluids**, changes in body fluids in Addison's disease, 985
- Fox, T. A.**: Hemorrhagic diatheses; analysis of 355 autopsy reports, 112
- Freyberg, R. H.**: Serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 13
- Friedländer Bacillus**: See Bacteria, mucosus capsulatus group
- Fusospirochetosis**; recovery of causative organisms from blood with report of 2 cases, 80
- Gallbladder**, calculi; chemical factors in formation of gallstones, 1037
- Gallstones**: See Gallbladder, calculi
- Gastric Ulcer**: See Peptic Ulcer
- Gastroenterology**, clinical aspects, 788
 physiologic aspects, 763
 review of literature from July 1940 to July 1941, 763
- Gastrointestinal Tract**: See also Intestines; Stomach; etc.
 infectious and parasitic diseases, 826
- Gibson, J. G., II.**: Response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
- Gilbert, G. G.**: Clinical lipid nephrosis with reference to its transformation into clinical and pathologic chronic glomerulonephritis, 591
- Gilligan, D. R.**: Acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
- Glomerulonephritis**: See under Nephritis
- Glycogen and carbohydrate metabolism**, 134
- Gonococci**, infections, 366
 infections, chemotherapy of, 333
- Gottlieb, J.**: Treatment of pneumococcal meningitis with sulfanilamide and sulfapyridine; statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum, 211
- Goudsmit, A., Jr.**: Acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
 Acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
- Greenspan, E. B.**: Rheumatic pneumonia, 1074
- Haemophilus Influenzae**: See Influenza
- Hammack, R. W.**: Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
- Hart, J. F.**: Blood sugar in case of complete hypophysectomy, 893
- Heart**: See also Blood, circulation; Endocarditis; etc.
 adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
 Diseases: See also Endocarditis; Myocarditis; etc.
 diseases; state of motor centers in circulatory insufficiency, 498
 prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
 prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
- Hematology**: See Blood
- Hemoglobin and Hemoglobin Compounds**: See Anemia; Blood; Erythrocytes; Hemoglobinuria
- Hemoglobinuria**, acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
- Hemorrhage**, response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
- Hepatitis**: See under Liver
- Hildebrand, A. G.**: Metabolism and diabetes; review of certain recent contributions, 134
- Holbrook, A. A.**: Blood picture in chickenpox, 294
- Hormones**: See Adrenal Preparations; Insulin; etc.
- Hunter, W. C.**: Thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
- Hydrophobia**: See Rabies
- Hyperinsulinism**: See under Insulin
- Hypertension**: See Blood pressure, high
- Hypertrophy**: See under names of organs and regions
- Hypoglycemia**: See Blood sugar
- Hypophysis**: See Pituitary Body
- Hypopituitarism**: See Pituitary Body
- Hypotension**: See Blood pressure, low
- Hypothermia**: See Temperature
- Icterus**: See Jaundice
- Industrial Diseases**, American Conference on Industrial Health, 846
- Infantile Paralysis**: See Poliomyelitis
- Infarction**: See under Heart
- Infection**: See also Bacteremia; and under names of bacteria, as Gonococci; Streptococci; etc.
 biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161

- Infectious Diseases:** See Communicable Diseases
- Influenza,** chemotherapy of, 335
- Insulin:** See also Diabetes Mellitus; Pancreas hyperinsulinism, 163
metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
review of literature, 155
shock therapy, 160
types of, 156
- Internal Secretions:** See Endocrine Glands
- Intestines:** See Gastrointestinal Tract
small and large intestine; review of literature, 812
- Iron,** "primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
- Islands of Langerhans:** See Pancreas
- Jaundice,** acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
- Jesser, J. H.:** Critical review of surgical treatment of vascular diseases, 636
Vascular diseases; seventh annual review, 599
- Jones, C. M.:** Gastroenterology; review of literature from July 1940 to July 1941, 763
- Jones, O. P.:** Transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
- Kala-Azar:** See Leishmaniasis
- Kean, B. H.:** Blood pressure studies on West Indians and Panamanians living on Isthmus of Panama, 466
- Keating, F. R.:** Diseases of adrenal glands; tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances, 1010
- Keefer, C. S.:** Significance of bacteremia caused by *Staphylococcus aureus*; study of 122 cases and review of literature concerned with experimental infection in animals, 851
- Keith, N. M.:** Acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
- Kepler, E. J.:** Diseases of adrenal glands; Addison's disease, 979
Diseases of adrenal glands; tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances, 1010
- Ketone Bodies:** See Blood, ketone bodies
- Kidneys,** abnormal function in Addison's disease, 984
adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
Diseases: See also Nephritis
diseases; clinical lipid nephrosis with reference to its transformation into clinical and pathologic chronic glomerulonephritis, 591
edema; acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
- Kidneys—Continued**
edema; acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
studies on "essential" hypertension; association of hypertension with organic renal disease, 261
- Kirshbaum, J. D.:** Tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
- Krygier, J. J.:** Primary pulmonary vascular sclerosis, 560
- LaDue, J. S.:** Bronchiolitis fibrosa obliterans; report of case, 663
- Landsteiner-Donath Phenomenon:** See Hemoglobinuria
- Langerhans' Islands:** See under Pancreas
- Langmuir, A. D.:** Immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
- Lectures, Salmon Memorial Lectures,** 1039
- Legs:** See also Extremities
shelter legs, 622
thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
- Leishmaniasis,** 361
- Leptospirosis,** 360
- Leukocytes,** blood picture in chickenpox, 294
- Levine, R.:** Origin of ketone bodies from fats and their regulation, 674
- Levine, S. A.:** Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
- Levy, H. A.:** Tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
- Lipase in Blood:** See under Blood
- Lipids:** See Blood, fats and lipoids
- Lipoid Nephrosis:** See Kidneys, diseases
- Lithiasis:** See Gallbladder, calculi
- Liver,** differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
Glycogen: See under Glycogen
hepatic function in patients with amyloidosis, 309
origin of ketone bodies from fats and their regulation, 674
vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
- Lord, J. W., Jr.:** Differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
- Loughlin, E. H.:** Treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
- Lungs:** See also Respiratory Tract; etc.
chemotherapy of acute pulmonary infections, 339
pulmonary cavitation associated with coccidioid infection, 1179
torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
- Lymphocytes,** blood picture in chickenpox, 294
in Meningitis: See Meningitis
- Lymphogranuloma Venereum,** 365
- Magiday, M.:** Blood sugar in case of complete hypophysectomy, 893
- Malnutrition:** See Nutrition
- Menadione:** See Jaundice

- Meningitis, chemotherapy of, 330
 lymphocytic choriomeningitis, 356
 pneumococcal; treatment with sulfanilamide and sulfapyridine; statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum, 211
- Meningococci: See under Meningitis
- Mental Diseases: See also Dementia Praecox; Neuroses and Psychoneuroses; etc.
 electric shock therapy for psychoses, 1236
 insulin shock therapy, 160
 neurologic approach to mental disorder, 1244
- Metabolism and diabetes; review of certain recent contributions, 134
 hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
 in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
 in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
 in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
- Milker's Nodules: See Cowpox
- Miller, E. B.: "Primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
- Mohr, C. F.: Biologic false positive serologic reactions in tests for syphilis; occurrence in normal persons, 898
 Biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
- Moore, J. E.: Biologic false positive serologic reactions in tests for syphilis; occurrence in normal persons, 898
 Biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
- Muscles, cervical rib and scalenus syndrome, 648
- Nephritis: See also Kidneys, diseases
 acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
 acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
 clinical lipid nephrosis with reference to its transformation into clinical and pathologic chronic glomerulonephritis, 591
 origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
- Nephrosis: See Kidneys, diseases; Nephritis
- Nerves: See Neuritis
- Nervous System, state of motor centers in circulatory insufficiency, 498
 torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
- Neuritis, diabetes and ocular conditions and neuritis, 152
- Neuropsychiatry, neurologic approach to mental disorder, 1244
 review for 1941, 1232
- Neuroses and Psychoneuroses: See also Mental Diseases; etc.
 war neuroses, 1232
- Neutrophils: See Leukocytes
- Nicolas-Favre's Disease: See Lymphogranuloma Venereum
- Nissl Bodies: See Rabies
- Nitrogen, metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
- Nutrition: See also Diet and Dietetics; Vitamins; etc.
 Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
- Obesity, 172
- Ogilvie, A. G.: Natural history of bronchiectasis; clinical, roentgenologic and pathologic study, 395
- Old Age, thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
- Oscillometry: See under Arteries
- Osmosis and Permeability, acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
- Owens, L. B.: Efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
- Pachydermitis: See Perioritis
- Pain, cause of so-called side ache that occurs in normal persons; personal observations, 94
- Paley, K.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
- Panamanians: See Races
- Pancreas and organs of secretion in diabetes mellitus, 147
 diagnosis of carcinoma of, 525
 pancreatic lesions and diabetes, 149
- Papper, E.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
- Paralysis, Infantile: See Poliomyelitis
- Patch Tests: See Anaphylaxis and Allergy
- Pearlman, A. W.: Hepatic function in patients with amyloidosis, 309
- Pecora, L. J.: Hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
- Peptic Ulcer, review of literature, 801
 treatment with posterior pituitary preparation, 172
- Perera, G. A.: Clinical and physiologic characteristics of chill, 241
- Periarteritis nodosa, 616
- Perioritis, acropachyderma with pachydermitis; report of case, 687
- Perlman, L.: Hemorrhagic diatheses; analysis of 355 autopsy reports, 112
- Pineal Gland, pinealectomies on young mammals, 176
- Pituitary Body, blood sugar in case of complete hypophysectomy, 893
 hypopituitarism and Simmonds' disease, 172
 review of literature, 165
 tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
- Pituitary Preparations, diabetes insipidus and antidiuretic principle of posterior lobe of pituitary gland, 170
 diabetogenic action of extracts of anterior lobe of pituitary gland, 166
 treatment of peptic ulcer with posterior pituitary preparation, 172
- Placenta, transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
- Plague, 353
- Pneumococci: See also Pneumonia
 immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
 Meningitis: See Meningitis
- Pneumonia, chemotherapy of pneumococcal lobar pneumonia, 328
 Friedländer, 348
 hemolytic streptococci, 347
 immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25

- Pneumonia—Continued
 pneumococcic, 344
 review of literature, 343
 rheumatic, 1074
 staphylococcic, 348
 treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
- Poisons and Poisoning: See under names of substances
- Poliomyelitis, 356
- Polyuria: See Diabetes Insipidus
- Power, M. H.: Acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
- Pregnancy, associated with diabetes mellitus, 142
- Proteins, acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
- Prothrombin: See Blood, coagulation
- Psittacosis, 362
- Psychoneurosis: See Neuroses and Psychoneuroses
- Raab, W.: Adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
- Rabies, 361
- Races, blood pressure studies on West Indians and Panamanians living on Isthmus of Panama, 466
- Ralli, E. P.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
- Ransmeier, J. C.: Direct cultivation of *Bacterium tularensis* from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
- Raynaud's Disease, 618
- Reed, E. A.: Immediate serum reaction in man; classification and analysis of reaction to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
- Reeves, D. L.: *Torula* infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
- Reflex, Carotid Sinus: See Carotid Sinus
- Reimann, H. A.: Infectious diseases; review of significant publications in 1940-1941, 325
- Respiratory Tract, chemotherapy of acute infections of, 335
 vaccines for infections of, 343
- Reticuloendothelial System: See Anemia; Jaundice; etc.
- Retinitis pigmentosa, 621
- Rheumatic Fever, 349
 rheumatic pneumonia, 1074
- Ribs, abnormalities; cervical rib and scalenus syndrome, 648
- Rickettsia; rickettsial diseases, 364
- Robertson, T. D.: Thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
- Robinson, G. W., Jr.: Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
- Rogers, E. S.: Immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
- Rosenbaum, F. F.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
 Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
- Rutstein, D. D.: Immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
- Ryneerson, E. H.: Metabolism and diabetes; review of certain recent contributions, 134
- Salmon Memorial Lectures, 1039
- Scalotomy: See Muscles
- Schaub, I. G.: Direct cultivation of *Bacterium tularensis* from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
- Schistosomiasis, 361
- Schizophrenia: See Dementia Praecox
- Schlesinger, M. J.: Multiple fresh coronary occlusions in patients with antecedent shock, 181
- Schroeder, H. A.: Studies on "essential" hypertension; association of hypertension with organic renal disease, 261
- Scleroderma; acrosclerosis, 620
- Scupham, G. W.: Vascular diseases; seventh annual review, 599
- Secretions, Internal: See Endocrine Glands
- Senility: See Old Age
- Sensitization: See Anaphylaxis and Allergy
- Serum: See Blood
- Shelton, P.: Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
- Shigella Dysenteriae: See Dysentery
- Shock, multiple fresh coronary occlusions in patients with antecedent shock, 181
- Shoulder, cervical rib and scalenus syndrome, 648
- Simmonds' Disease: See under Pituitary Body
- Simonson, E.: State of motor centers in circulatory insufficiency, 498
- Sinus, Carotid: See Carotid Sinus
- Skin, acropachyderma with pachydermatitis; report of case, 687
- Skinner, D.: Significance of bacteremia caused by *Staphylococcus aureus*; study of 122 cases and review of literature concerned with experimental infection in animals, 851
- Smith, F. V., Jr.: Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
- Sneeden, V. D.: Thrombosis of deep veins of legs; its clinical significance as exemplified in 351 autopsies, 1
- Snyder, G. A. C.: Thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
- Societies, American Conference on Industrial Health, 846
 Association of Military Surgeons of United States, 661
 Mississippi Valley Medical Society, 369
- Sodium, Bicarbonate: See Ketosis
 metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
- Soskin, S.: Origin of ketone bodies from fats and their regulation, 674
- Spaeth, R.: Therapy of tetanus; study of 276 cases, 1133
- Spherocytosis: See under Erythrocytes
- Spitz, S. H.: Treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
- Staphylococci, chemotherapy of staphylococcic infections, 333
 significance of bacteremia caused by *Staphylococcus aureus*; study of 122 cases and review of literature concerned with experimental infection in animals, 851
- Stead, E. A., Jr.: Response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578

- Steele, C. W.: Treatment of pneumococcal meningitis with sulfanilamide and sulapyridine; statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum, 211
- Steele, J. M.: Studies on "essential" hypertension; association of hypertension with organic renal disease, 261
- Sterilization of air, 367
- Stomach: See also Gastrointestinal Tract
transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
- Ulcers: See Peptic Ulcer
- Stools: See Feces
- Streptococci, chemotherapy of hemolytic streptococcal infection, 332
- rheumatic fever, 349
- Sugar in Blood: See Blood, sugar
- Sulfanilamide and Sulfanilamide Derivatives, Therapy: See under Communicable Diseases; Meningitis; Pneumonia; etc.
- Sulapyridine, Therapy: See Meningitis
- Suprarenal Preparations: See Adrenal Preparations
- Suprarenals: See Adrenals
- Surgery, military; Association of Military Surgeons of United States, 661
- Sympathectomy: See Extremities, blood supply
- Syphilis: See also under names of organs and regions
biologic false positive serologic reaction in tests for syphilis; occurrence in normal persons, 898
biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
- Talbott, J. H.: Hypothermia; report of case in which patient died during therapeutic reduction of body temperature with metabolic and pathologic studies, 1120
- Temperature: See also Cold
cutaneous, 610
hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
- Tetanus, 352
therapy; study of 276 cases, 1133
- Thromboangiitis obliterans, 614
- Thrombosis: See also Embolism and embolism, 612
arterial occlusions, 641
multiple fresh coronary occlusions in patients with antecedent shock, 181
of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
therapy, 623
venous occlusions, 638
- Tiber, A. M.: Hepatic function in patients with amyloidosis, 309
- Tick Fevers; Colorado tick fever, 364
- Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
- Toxoplasmosis, 362
- Trauma, traumatic factor in diabetes mellitus, 141
- Trypanosomiasis; Chagas' disease, 363
- Tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
- Tuberculosis: See under names of organs and regions, as Pituitary Body; etc.
- Tularemia, direct cultivation of *Bacterium tularensis* from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
- Tumors: See under names of organs and regions, as Adrenals; etc.
- Typhoid, 351
- Ulcers, Peptic: See Peptic Ulcer
- Uranium Nephritis: See under Nephritis
- Urine: See also Diuresis and Diuretics; etc.
acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
- Urobilinogen: See under Urine
- Van Dellen, T. R.: Vascular diseases; seventh annual review, 599
- Vasomotor System: See Arteries; Blood vessels; Capillaries; Veins
- Veins: See also Blood vessels; Embolism; Thrombosis
exercise test, 622
- Venous Pressure: See Blood pressure
- Ventriculin: See under Stomach
- Viruses, neurotropic, 355
- Vitamins: See also Deficiency Diseases; Diet and Dietetics; etc.
A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
deficiency and metabolism of carbohydrate, 153
- K: See Blood, coagulation
- War: See also Air Raids; Surgery, military; etc.
neuroses, 1232
- Watson, C. J.: Determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
- Williams, R. H.: Fusospirochetosis; recovery of causative organisms from blood with report of 2 cases, 80
- Willson, D. M.: Diseases of adrenal glands; Addison's disease, 979
- Winn, W. A.: Pulmonary cavitation associated with coccidioid infection, 1179
- Winship, T. O.: Elliptic erythrocytes in man, 1043
- Wright, J.: Efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
- Wyandt, H.: Elliptic erythrocytes in man, 1043
- Zoll, P. M.: Multiple fresh coronary occlusions in patients with antecedent shock, 181

